SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin 500 mg, Powder for Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg clarithromycin (as lactobionate).

Each millilitre of final reconstituted/diluted solution for infusion contains 2 mg clarithromycin (as lactobionate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Concentrate for Solution for Infusion.

White crystalline powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clarithromycin 500 mg, powder for concentrate for solution for infusion is indicated when parenteral therapy is required for treatment of infections, caused by clarithromycin-susceptible organisms in the following conditions:

- Community acquired pneumonia
- Acute exacerbation of chronic bronchitis
- Acute bacterial sinusitis (adequately diagnosed)
- Bacterial pharyngitis and tonsillitis
- Skin and soft tissue infections

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

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

4.2 Posology and method of administration

Posology

Adults and adolescents: The recommended dose is 1.0 gram daily of Clarithromycin powder for concentrate for solution for infusion (appropriately diluted as described below), administered as two separate 500mg doses at 12 hourly intervals.

Elderly: Same as for adults.

Renal Impairment:

Patients with severe renal impairment, with creatinine clearance less than 30ml/min, the dosage of clarithromycin should be reduced to one half of the normal recommended dose.

Paediatric population

Children aged 12 or less:

Use of Clarithromycin powder for concentrate for solution for infusion is not recommended for children younger than 12 years. Use clarithromycin Paediatric Suspension.

Children older than 12 years: As for adults.

Recommended administration:

Clarithromycin 500 mg, powder for concentrate for solution for infusion should be administered into one of the larger proximal veins as an IV infusion over 60 minutes, using a solution concentration of about 2mg/ml. Clarithromycin should not be given as a bolus or an intramuscular injection.

Method of administration

For intravenous administration only.

Clarithromycin may be given for 2 to 5 days by intravenous infusion, however, patients should be switched to the oral therapy should longer term treatment be required.

For instructions on dilution of the medicinal product before administration, see section 6.6

4.3 Contraindications

Hypersensitivity to the active substance or macrolide antibiotic drugs or to any of the excipients listed in section 6.1.

Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated, as this may result in ergot toxicity. (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 drugs is contraindicated: astemizole, cisapride, domperidone, pimozide and 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 should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointe (see sections 4.4 and 4.5).

Concomitant administration with ticagrelor, ivabradine 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).

Treatment with these agents should be discontinued during clarithromycin treatment (see section 4.4).

Clarithromycin should not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of the QT interval).

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

Clarithromycin should not be used concomitantly in patients taking colchicine (see sections 4.4 and 4.5).

Concomitant administration of clarithromycin and lomitapide is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

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 coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia
- Patients with electrolyte disturbances. 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 terfendine 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.

Use during pregnancy

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).

Renal and hepatic impairment

Caution is advised in patients with moderate to severe renal insufficiency (see section 4.2).

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

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. 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.

Antibiotic-associated diarrhoea

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of C. difficile.

"CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents" Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

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

Colchicine

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).

Drug interactions

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.

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

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

Hypersensitivity

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

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

Oral hypoglycaemic agents/Insulin

The concomitant use of clarithromycin and oral hypoglycaemic agents and/or insulin can result in significant hypoglycaemia. With certain hypoglycaemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia when used concomitantly. Careful monitoring of glucose is recommended.

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, apixaban and edoxaban, particularly to patients at high risk of bleeding (see section 4.5).

Long term use and resistance

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

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

Attention should 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 interaction

The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:

Cisapride, domperidone, pimozide, astemizole and terfenadine:

Clarithromycin is considered to be an inhibitor of cisapride and terfenadine metabolism with a twofold up to three-fold increase of terfenadine plasma levels. 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 symptoms have been reported in patients taking pimozide and clarithromycin concomitantly. Concomitant administration of clarithromycin and terfenadine, cisapride, pimozide and astemizole is contraindicated (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.

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 ischaemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated (see section 4.3).

Effects of other medicinal products on clarithromycin

Drugs that are CYP3A inducers (such as rifampicine, phenytoin, carbamazepine, phenobarbital, products containing St. John Wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. If clarithromycin is clearly indicated, it may be necessary to increase the dose of clarithromycin, and closely monitor its efficacy and safety. Further, 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 relevant Summary of Product Characteristics of the administered CYP3A inducer). 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-(R)-hydroxy-clarithromycin (14-OH-clarithromycin), a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

A 39% reduction in AUC for clarithromycin and a 34% increase in AUC for the active 14-OHhydroxy metabolite have been seen when clarithromycin was used concomitantly with the CYP3A4 inducer efavirenz.

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.

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax, increased by 31%, Cmin increased 182% and AUC increased by 77%, with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14 -OH-clarithromycin was noted . Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with creatinine clearance CL_{CR} of 30 to 60 ml/min (0.5 – 1 ml/s) the dose of clarithromycin should be reduced by 50%.For patients with creatinine clearance CL_{CR} of <30 ml/min (<0.5 ml/s) the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 gm/day should not be co-administered with ritonavir.

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

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 drugs known to be CYP3A 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, ibrutinib ,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.

Antiarrhythmics

There have been post-marketed reports of Torsades de pointes occurring with the concurrent use of clarithromycin and quinidine or disopyramid. Electrocardiograms should be monitored for QTc prolongation during co-administration of clarithromycin with these drugs. Serum levels of quinidine and disopyramid should be monitored during clarithromycin therapy. A dose adjustment may be necessary. If

clarithromycin is given to patients who are treated with other products which may prolong QT interval, cautions should be exercised (see section 4.4).

Omeprazole

Although the plasma concentrations of clarithromycin and omeprazole may be increased when they are administered concurrently, no dose adjustment is necessary. Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (Cmax, AUC0-24, and t1/2 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.

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

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 metabolizer population.

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

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. In 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 metabolised via CYP3A4, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A4 for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

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

Corticosteroids

ncomitant use of clarithromycin with systemic and inhaled corticosteroids that are primarily metabolised by CYP3A due to the potential for increased systemic exposure to corticosteroids. If concomitant use occurs, patients should be closely monitored for systemic corticosteroid undesirable effects.

Direct acting oral anticoagulants (DOACs)

The DOACs dabigatran and edoxaban are substrates 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).

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

The use of clarithromycin is also contraindicated with ergot alkaloids, oral midazolam, colchicine, ticagrelor, ivabradine and ranolazine (see section 4.3).

Other drug interactions

Hydroxychloroquine and chloroquine:

Clarithromycin should be used with caution in patients receiving these medicines known to prolong the QT interval due to the potential to induce cardiac arrhythmia and serious adverse cardiovascular events.

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine (see section 4.3 and 4.4).

Digoxin

Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should

be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV infected 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-OHclarithromycin, 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 coadministered 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 bid) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in steady-state AUC and Cmax values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and Cmax values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are coadministered 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 the saquinavir /ritonavir therapy. When saquinavir is coadministered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see Section 4.5-Ritonavir).

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

HMG-CoA reductase inhibitors

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.

Cyclosporin, tacrolimus and sirolimus

Concomitant administration of the oral form of clarithromycin with cyclosporin or tacrolimus results in more than a two-fold increase of Cmin plasma concentrations of cyclosporin and tacrolimus. Similar effects can also be expected with sirolimus.

Plasma levels of cyclosporin, tacrolimus or sirolimus should be thoroughly monitored when commencing treatment with clarithromycin in patients on any of the above mentioned immunosuppresants, and their doses should be decreased, if necessary.

Clarithromycin discontinuation in those patients also requires a thorough monitoring of cyclosporin, tacrolimus or sirolimus plasma levels to guide dose adjustment.

Warfarin

The use of Clarithromycin in patients receiving warfarin may result in a potentiation of the effects of warfarin. Prothrombin time should be frequently monitored in these patients.

The use of clarithromycin in patients concurrently taking other drugs metabolized by the cytochrome p450 system (e.g. cilostazol, methylprednisolone, sildenafil, vinblastine) may be associated with elevations in serum levels of these other medicinal products.

Clarithromycin has been shown not to interact with oral contraceptives.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of Clarithromycin during pregnancy and breast-feeding of infants 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 risk (see section 5.3).

Breast-feeding

The safety of clarithromycin for using during breast-feeding of infants has not been established. 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

In the rat, fertility studies have not shown any evidence of harmful effects (see section 5.3).

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 peadiatric 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 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), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000) and not known: (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 to <1/1,000)**	**Very rare (<1/10,000)**	**Not Known cannot be estimated from the available data**
Infections and infestations	---	Oral monilia (candidiasis), prolonged use may result in the overgrowth of non-susceptible	Cellulitis[1], candidiasis, gastroenteritis[2], infection[3], vaginal infection	---	---	Pseudomembranous colitis, erysipelas, erythrasma

		organisms				
Blood and Lymphatic system disorders	---	---	Leucopenia, neutropenia[4], thrombocythaemia[3], eosinophilia[4]	---	Thrombocytopenia	Agranulocytosis
Immune System Disorders	---	---	Anaphylactoid reaction[1], hypersensitivity Allergic reactions ranging from urticaria to mild skin eruptions and angioedema to anaphylaxis.	---	---	Anaphylactic reaction
Metabolism and nutrition disorders	---	---	Anorexia, decreased appetite	---	---	Hypoglycaemia[6]
Psychiatric disorders	---	Insomnia	Anxiety Nervousness[3]	---		Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania.
Nervous system disorders	---	Headache, smell alteration Dysgeusia	Loss of consciousness[1], dyskinesia[1], somnolence[7], tremor	convulsions	Paraesthesia, vertigo, dizziness	Ageusia, parosmia, anosmia

Eye disorders	---	---	---	---	Uveitis mainly in patients treated with concomitant rifabutin, most of these were reversible	---
Ear and Labyrinth Disorders	---	---	Vertigo, hearing impaired	Tinnitus	Reversible hearing loss	Deafness
Cardiac Disorders	---	---	Cardiac arrest[1], atrial fibrillation[1], extrasystoles[1], palpitations, QT prolongation	---	---	Ventricular fibrillation Ventricular tachycardia, Torsade de pointes.
Vascular disorders	---	Vasodilation[1]	---	---	---	Haemorrhage[9]
Respiratory, thoracic and mediastinal disorder	---	---	Asthma[1],epistaxis[2], pulmonary embolism	---	---	---
Gastrointestinal disorders	---	Nausea, vomiting, diarrhoea[10], dyspepsia, Abdominal pain, Stomatitis, Glossitis,	Oesophagitis[1], gastrooesophageal reflux disease[2], gastritis, proctalgia[2], abdominal	---	Pancreatitis, Pseudomembranous colitis has been reported very rarely with clarithromycin and may	

		tooth and tongue discolouration and taste perversion, i.e. metallic or bitter taste.	distension[4], constipation, dry mouth, eructation, flatulence,		range in severity from mild to life threatening.	
Hepato-biliary disorders	---	Liver function test abnormal	Hepatic dysfunction, which is usually transient and reversible, hepatitis[4] and cholestasis[4] with or without jaundice, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased[4]	---	Fatal hepatic failure has been reported particularly in patients with pre-existing liver disease or taking other hepatotoxic medicinal products.	Hepatic failure[11], jaundice hepatocellular
Skin and subcutaneous tissue disorders	---	Rash, hyperhidrosis	Exanthema. Urticaria, Dermatitis bullous[1], pruritus, rash maculo-papular[3]	---	Severe cutaneous adverse reactions (SCAR): Stevens-Johnson syndrome / Toxic epidermal necrolysis	Severe cutaneous adverse reactions (SCAR): Drug rash with eosinophilia and systemic symptoms (DRESS), acne, acute generalised exanthematous pustulosis

						(AGEP)
Musculoskeletal and connective tissue disorders	---	---	Arthralgia, Myalgia[2], Muscle spasms[3], musculoskeletal stiffness[1]	---	---	Rhabdomyolysis[2,12], myopathy
Renal & urinary disorders	---	---	Blood creatinine increased[1], blood urea increased[1]	---	Interstitial nephritis, Renal failure	Nephritis interstitial
General disorders and administration site conditions	Injection-site phlebitis[1]	Injection-site inflammation[1], tenderness and pain[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]	---	---	---
Investigations	---	Elevated BUN	Elevated serum creatinine, altered liver function tests (increased transaminase levels), prolonged prothrombin time (increased INR), albumin globulin ratio abnormal[1], blood alkaline phosphatase increased[4], blood lactate	---	Hypoglycaemia has been observed especially after concomitant administration with antidiabetic medicinal products and insulin	International normalised ratio increased[9], prothrombin time prolonged[9], urine color abnormal

			dehydrogenase increased[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

[10,11,12]See section a)

[6,7,9]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 very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications (see section 4.4).

A special attention to diarrhoea should be paid as 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. (see section 4.4)

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

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

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents (see section 4.4).

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

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

There have been rare reports of hypoglycaemia, some of which have occurred

in patients on concomitant oral hypoglycaemic agents or insulin (see section 4.4 and 4.5).

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested (see section 4.5).

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

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

d. Paediatric populations

Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

e. Other special populations

Immunocompromised patients

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

There is no experience of overdosage after IV 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.

Symptoms of overdose may largely correspond to the profile of adverse reactions, that could be treated by gastric lavage and supportive measures.

Management

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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(R)-hydroxy metabolite of clarithromycin, a product of the metabolisation of the parent substance which is found in humans, also has an antibacterial effect. The MICs of this metabolite are equal or twofold higher than the MICs of the parent compound except for H. influenzae where the 14- hydroxy metabolite is two-fold more active than the parent compound.

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

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 (S_B) (so called MLS_B 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.

EUCAST Breakpoints: Macrolides, lincosamides, streptogramins - EUCAST clinical MIC breakpoints 2008-06-19 (v 1.2)

		Species-related breakpoints (S≤/R>)	**Non-**

		Enterobacteriaceae	*Pseudomonas*	*Acinetobacter*	*Staphylococcus*	*Enterococcus*	*Streptococcus A,B,C,G*	*S.pneumoniae*	*Other streptococci*	*H.influenzae*	*M.catarr-halis*	*N.gonorrhoeae*	*N.meningitidis*	*Gram-negative anaerobes*	*Gram-positive anaerobes*	*Helicobacter pylori*	
Clarithromycin[B,C]	RD	--	--	--	1/2	--	0.25/ 0.5	0.25/ 0.5	IE	1/32[D]	0.25/ 0.5	--	--	--	--	0.25 / 0.5	IE

A. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table or footnotes However, pharmacodynamic data for calculation of macrolide, lincosamines and streptogramins non-species related breakpoints are not robust, hence IE.
B. Erythromycin can be used to determine the susceptibility of the listed bacteria to the other macrolides (azithromycin, clarithromycin and roxithromycin). Macrolides administered intravenously are active against Legionella pneumophila (erythromycin MIC ≤1 mg/L for wild
type isolates). Macrolides have been used in the treatment of infections with Campylobacter jejuni (erythromycin MIC ≤4 mg/L for wild type isolates). Azithromycin has been used in the treatment of infections with S. typhi (MIC ≤16 mg/L for wild type isolates) and Shigella spp.
C. Clarithromycin is used for the eradication of H. pylori (MIC ≤0.25 mg/L for wild type isolates).
D. The correlation between H. influenzae macrolide MICs and clinical outcome is weak. Therefore, breakpoints for macrolides and related antibiotics were set to categorise wild type H. influenzae as intermediate.

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

Clarithromycin 500 mg/vial Powder for Solution for Injection 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.

5.2 Pharmacokinetic properties

The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism as indicated by lower bioavailability of the metabolite following IV administration. Following IV administration the blood levels of clarithromycin achieved are well in excess of the MIC 90s 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 due to saturation of hepatic metabolism at high doses; 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.

<u>Distribution</u>
Clarithromycin penetrates rapidly into various body tissues and fluids. In adults the volume of distribution ranges from 200 to 400 litres. Tissue concentrations in lung and tonsils have been found to be several times higher than plasma levels.
Clarithromycin is 80% bound to plasma proteins at therapeutic levels.

<u>Biotransformation and Elimination</u>
Clarithromycin is metabolised in the liver by the cytochrome P-450 enzyme system quickly and to a large extent. The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism as indicated by lower bioavailability of the metabolite following IV administration.

Following a single 500mg IV dose over 60 minutes, about 33% clarithromycin and 11% 14-hydroxyclarithromycin is excreted in the urine at 24 hours.

In patients with renal impairment an increase of clarithromycin plasma levels and its active metabolite has been observed.

5.3 Preclinical safety data

Fertility, Reproduction and Teratogenicity

No fertility studies with intravenous (I.V.) administration of clarithromycin have been conducted. Oral fertility and reproduction studies in rats have shown no adverse effects.

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 Sprague-Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomolgous monkeys failed to demonstrate any teratogenicity from clarithromycin.

Intravenous embryo-foetal toxicity studies demonstrated no evidence of embryo-foetal toxicity or teratogenicity at maternally toxic dosages up to 160 mg/kg/day in rats (TILDE OPERATOR (8764)1.5 times the maximum recommended human dose (MRHD) on a mg/m2 basis) and 30 mg/kg/day in rabbits (TILDE OPERATOR (8764)0.6 times the MRHD on a mg/m2 basis). In rabbits, in utero foetal loss occurred at an intravenous dose of 33 mg/m2, which is 17 times less than the MRHD of 618 mg/m2. Oral teratogenicity studies in rats, rabbits and monkeys failed to demonstrate any teratogenicity from clarithromycin at the highest doses tested up to 1.5, 2.4 and 1.5 times the MRHD of 1 g/day P.O. on a mg/m2 basis in the respective species. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactobionic acid.

6.2 Incompatibilities

None known.

However, Clarithromycin 500 mg, powder for concentrate for solution for infusion, should only be diluted with the diluents recommended.

6.3 Shelf life

Unopened vials: 4 years

After reconstitution in 10 ml water for injections:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and for 48 hours at 5°C.
From a microbiological point of view, the product should be diluted immediately. If not diluted 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° C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

After dilution to 250 ml in an appropriate diluent:
Chemical and physical in-use stability has been demonstrated for 6 hours at 25°C and for 48 hours at 5°C.

From a microbiological point of view, the solution for infusion 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° C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30° C.

Store in the original container in order to protect from light.

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

6.5 Nature and contents of container

26 ml, type I clear glass vial of European Pharmacopoeia quality, sealed with a type I bromobutyl stopper of European Pharmacopoeia quality and an aluminium cap.

Vials are packed in units of 1, 4 and 6. Pack size 500mg.
Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

Clarithromycin 500 mg, powder for concentrate for solution for infusion should be administered into one of the larger proximal veins as an IV infusion over 60 minutes, using a solution concentration of about 2mg/ml. Clarithromycin should not be given as a bolus or by intramuscular injection.

For single use only.

A. Preparation of the vial solution

Inject 10 ml of water for injections into a vial containing the product. Shake until the vial contents have dissolved. Use only water for injections for the dissolution. Other solvents may result in the formation of a precipitate. Do not use solutions of inorganic salts or solutions containing preservatives.
1 ml of the vial solution prepared in this way contains 50 mg clarithromycin lactobionate.
For storage conditions for the reconstituted medicinal product see Section 6.3

B. Preparation of infusion solution

Make up 10ml of the vial solution prepared in step A (containing 500 mg clarithromycin lactobionate) to 250 ml using one of the following solutions: 0.9% Sodium Chloride, 5% Dextrose, 5% Dextrose in 0.3% sodium chloride, 5% Dextrose in 0.45% sodium chloride, 5% Dextrose in Ringer's lactate solution and Ringer's lactate solution.

1ml of the infusion solution prepared in this way contains 2mg clarithromycin lactobionate.
For storage conditions for the diluted medicinal product see Section 6.3

IMPORTANT: BOTH DILUENT STEPS (A and B) SHOULD BE COMPLETED BEFORE USE.

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

7 MARKETING AUTHORISATION HOLDER

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