



APO-CLARITHROMYCIN

1. PRODUCT NAME

APO-CLARITHROMYCIN (250mg and 500mg film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 250mg film coated tablet contains 250mg of clarithromycin.

Each 500mg film coated tablet contains 500mg of clarithromycin.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Apo-Clarithromycin 250 mg tablets are pale yellow, oval, biconvex, film-coated tablets engraved "CLA250" on one side, "APO" on the other side.

Apo-Clarithromycin 500 mg tablets are pale yellow, capsule-shaped, biconvex, film-coated tablets engraved "CLA500" on one side, "APO" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clarithromycin tablets are indicated for treatment of infections caused by susceptible organisms. Such infections include:

- Respiratory tract infections including bronchitis, pneumonia, tonsillitis, sinusitis and pharyngitis (see section 4.4 and 5.1 regarding Sensitivity testing).
- Skin and soft tissue infections such as folliculitis, cellulitis and erysipelas (see section 4.4 and 5.1 regarding Sensitivity testing).
- Disseminated or localized mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare*. Localized infections due to *Mycobacterium chelonae*, *Mycobacterium fortuitum*, or *Mycobacterium kansasii*.
- Prevention of disseminated *Mycobacterium avium* complex infection in HIV-infected patients with CD4 lymphocyte counts less than or equal to 100/mm³.
- Clarithromycin in the presence of acid suppression is indicated for the treatment of duodenal ulcer and in reducing the rate of ulcer recurrence (see section 5.1).

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

4.2 Dose and method of administration

Dose

Do not halve tablet.

Adults

The usual recommended dosage of clarithromycin in adults and children 12 years of age or older is one 250 mg tablet twice daily. In more severe infections, the dosage can be increased to 500 mg twice daily. The usual duration of therapy is 5 to 14 days, excluding treatment of community acquired pneumonia and sinusitis which require 6 to 14 days of therapy.

Special populations

Renal impairment

In patients with renal impairment with creatinine clearance less than 30 mL/min, the dosage of clarithromycin should be reduced by one-half, i.e., 250 mg once daily, or 250 mg twice daily in more severe infections. Dosage should not be continued beyond 14 days in these patients.

Paediatric

The use of clarithromycin tablets has not been studied in children less than 12 years of age.

Dosage in patients with mycobacterial infections

The recommended starting dose for adults with disseminated or localized mycobacterial infections (*M. avium*, *M. intracellulare*, *M. chelonae*, *M. fortuitum*, *M. kansasii*) is 500 mg twice daily.

Treatment of disseminated MAC infections in AIDs patients should be continued as long as clinical and microbiological benefit is demonstrated. Clarithromycin should be used in conjunction with other antimycobacterial agents.

Treatment of other nontuberculous mycobacterial infections should continue at the discretion of the physician.

Dosage for MAC prophylaxis

The recommended dosage of clarithromycin in adults is 500 mg twice daily.

In duodenal ulcer associated with *H. pylori*, the recommended dose of clarithromycin is:

Triple therapy regimen

Clarithromycin 500 mg b.i.d in conjunction with amoxicillin 1000 mg b.i.d and omeprazole 20 mg b.i.d. for 7 to 10 days.

Clarithromycin 500 mg, omeprazole 20 mg and amoxicillin 1000 mg all twice daily for one week.

Clarithromycin 500 mg, amoxicillin 1000 mg, pantoprazole 40 mg all twice daily for one week.

Dual therapy regimen

Clarithromycin 500 mg t.i.d. in conjunction with omeprazole 40 mg daily for 14 days, followed by omeprazole 20 mg or 40 mg daily for an additional 14 days.

4.3 Contraindications

- Hypersensitivity to macrolide antibiotics or any of its excipients. Allergic or hypersensitivity reactions should be managed by prompt supportive measures.
- Concomitant administration of clarithromycin and any of the following medicines is contraindicated: astemizole, cisapride, domperidone, pimozide, terfenadine as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and *torsades de pointes* (see section 4.4).
- 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 section 4.4).
- Clarithromycin should not be given to patients with hypokalaemia (risk of prolongation of QT-time).
- Concomitant administration of clarithromycin and ergot alkaloids (e.g., ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity.
- Concomitant administration of clarithromycin and oral midazolam is contraindicated (see section 4.5).
- Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
- Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolised by CYP3A4 (lovastatin or simvastatin) due to the increased risk of myopathy, including rhabdomyolysis (see section 4.4).
- Clarithromycin (and other strong CYP3A4 inhibitors) should not be used concomitantly with colchicine (see section 4.4 and 4.5).
- Concomitant administration with ticagrelor or ranolazine is contraindicated.

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.

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

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

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 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, domperidone, pimozone 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.

Pseudomembranous colitis

Pseudomembranous colitis has been reported with nearly all anti-bacterial 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.

Hepatic and renal impairment

Clarithromycin is principally metabolized by the liver. Therefore, caution should be exercised in administering clarithromycin to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.

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. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Myasthenia gravis

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

Triazolobenzodiazepines

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

Ototoxic drugs

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 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 generalized exanthematous pustulosis (AGEP), Stevens Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS)), and Henocho-Schonlein purpura, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see section 4.5).

Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin

Oral anticoagulants

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.

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.

As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors. Patients should be monitored for signs and symptoms of myopathy.

4.5 Interactions with other medicines and other forms of interaction

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

Astemizole, cisapride, domperidone, pimozone 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 torsade de pointes. Similar effects have been observed in patients taking clarithromycin and pimozone concomitantly (see section 4.3).

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsade de pointes (see section 4.3). In one study in 14 healthy

volunteers, the concomitant administration of clarithromycin (tablets) and terfenadine resulted in a 2 to 3-fold increase in the serum level of the acid metabolite of terfenadine and in the 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.

HMG-CoA reductase inhibitors (statins)

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

Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Rare reports of rhabdomyolysis have also been reported in patients taking 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. Patients should be monitored for signs and symptoms of myopathy.

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 ischemia 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.

Effects of other medicinal products on clarithromycin

Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inducer administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

Efavirenz, nevirapine, rifampicin and rifabutin

Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin and rifabutin 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 adult volunteers led to increases in the mean steady-state minimum clarithromycin concentration (C_{min}) and area under the curve (AUC) of 33% and 18%, respectively. Steady-state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every 8 hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin C_{max} increased by 31%, C_{min} increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-[R]-hydroxy-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR < 30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 g/day should not be co-administered with ritonavir.

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 medicine interactions).

Effects of clarithromycin on other medicinal products

Antiarrhythmics

There have been postmarketed reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during co-administration of clarithromycin with these medicines. Serum levels of these medications should be monitored during clarithromycin therapy.

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

Oral hypoglycemic agents/insulin

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

CYP3A-based interactions

Co-administration of clarithromycin, known to inhibit CYP3A, and a medicine primarily metabolised by CYP3A may be associated with elevations in medicine concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant medicine.

Clarithromycin should be used with caution in patients receiving treatment with other medicines 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 medicines primarily metabolised by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

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

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} , AUC₀₋₂₄ 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 medicines are co-administered with clarithromycin.

Theophylline, carbamazepine

Results of clinical studies indicate there was a modest but statistically significant ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels when either of these medicines are administered concomitantly with clarithromycin. Serum theophylline or carbamazepine levels should be monitored in patients receiving concomitant clarithromycin.

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. triazolam and alprazolam) and related benzodiazepines (e.g. midazolam)

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

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

Other medicine interactions

Aminoglycosides

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

Colchicine

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

Digoxin

When clarithromycin and digoxin are administered together, inhibition of P-glycoprotein (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 concentration should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. This interaction does not appear to occur in paediatric HIV-infected patients taking a clarithromycin suspension formulation concurrently with zidovudine or dideoxyinosine. Because clarithromycin appears to interfere with the absorption in adults of simultaneously administered oral zidovudine, this interaction would most likely not be a problem when clarithromycin is administered intravenously. This interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine.

Phenytoin and valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolized by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.

Bi-directional medicine interactions

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional medicine 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.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bi-directional medicine 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 medicine interaction. Concomitant administration of clarithromycin (500 mg b.i.d) and saquinavir (soft gelatin capsules, 1200 mg t.i.d.) 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 medicines are co-administered for a limited time at the doses/formulations studied. Observations from medicine interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from medicine 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 Effects of other medicinal products on clarithromycin).

Oral contraceptives

There is no loss of efficacy of oral contraceptives when used in combination with clarithromycin.

Calcium channel blockers

Acute kidney injury has been reported in patients using clarithromycin and calcium channel blockers (CCBs) metabolised by CYP3A4 (e.g. verapamil, amlodipine, diltiazem), although the causal association cannot be established. Most of these cases involved elderly patients 65 years of age or older. Additionally, caution is advised regarding the concomitant administration of clarithromycin and CCBs metabolized by CYP3A4 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category B3. There are no adequate and well-controlled studies in pregnant women. The safety of clarithromycin for use during pregnancy has not been established. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

Breast-feeding

The safety of clarithromycin for use during breast-feeding of infants has not been established. Clarithromycin is excreted into human breast milk.

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 machinery

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

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and pediatric populations are abdominal pain, diarrhea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics.

There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without preexisting mycobacterial infections.

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin.

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The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) 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.

Table 3				
Adverse Reactions				
System Organ Class	Very common $\geq 1/10$	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1,000$ to $< 1/100$	Not Known* (cannot be estimated from the available data)
Infections and infestations			Cellulitis ¹ , candidiasis, infection ² , vaginal infection	Pseudomembranous colitis, erysipelas, erythrasma
Blood and lymphatic system			Leukopenia, neutropenia ³ , Thrombocythemia ² , Eosinophilia ³	Agranulocytosis, thrombocytopenia
Immune system disorders			Anaphylactoid reaction ¹ , hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	Hypoglycaemia
Psychiatric disorders		Insomnia	Anxiety, nervousness ² , Screaming ²	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache	Loss of consciousness ¹ , dyskinesia ¹ , dizziness, somnolence, tremor	Convulsion, ageusia, parosmia, Anosmia paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest ¹ , atrial fibrillation ¹ , electrocardiogram QT prolonged, extrasystoles ¹ , palpitations	Torsade de pointes, ventricular tachycardia, ventricular fibrillation

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Vascular disorders		Vasodilation ¹		Haemorrhage
Respiratory, thoracic and mediastinal disorder			Asthma ¹ , pulmonary embolism ¹	
Gastrointestinal disorders		Diarrhea, vomiting, dyspepsia, nausea, abdominal pain	Esophagitis ¹ , gastroesophageal, gastritis, stomatitis, glossitis, abdominal distension ³ , constipation, dry mouth, eructation, flatulence	Pancreatitis acute, tongue discolouration, tooth discolouration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis ³ , hepatitis ³ , alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased ⁴	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous ¹ , pruritus, urticaria, rash maculopapular ³	Severe cutaneous adverse reactions (SCAR) (e.g. acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS)), acne, Henoch-Schonlein Purpura
Musculoskeletal and connective tissue disorders			Muscle spasms ² , musculoskeletal stiffness ¹ , myalgia	Rhabdomyolysis**, myopathy
Renal and urinary disorders			Blood creatinine increased ¹ , blood urea increased ¹	Renal failure, nephritis interstitial

General disorders and administration site conditions	Injection site phlebitis ¹	Injection site pain ¹ , Injection site inflammation ¹	Malaise ³ , pyrexia ² , asthenia, chest pain ³ , chills ³ , fatigue ³	
Investigations			Albumin globulin ratio abnormal ¹ , blood alkaline phosphatase increased ³ , blood lactate dehydrogenase increased ³	International normalised ratio increased, prothrombin time prolonged, urine colour abnormal
<p>*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.</p> <p>**In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with other drugs known to be associated with rhabdomyolysis (such as statins, fibrates, colchicine or allopurinol).</p> <p>¹ ADRs reported only for the Powder for Solution for Injection formulation</p> <p>² ADRs reported only for the Granules for Oral Suspension formulation</p> <p>³ ADRs reported only for the Immediate-Release Tablets formulation</p>				

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 HIV disease or intercurrent illness.

In adult patients, the most frequently reported adverse events by patients treated with total daily doses of 1,000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance, SGOT and SGPT elevations. Additional low-frequency events included dyspnoea, insomnia, and dry mouth.

In these immunocompromised patients evaluations of laboratory values were made by analyzing those values outside the seriously abnormal level (i.e., the extreme high or low limit) for the specified test. On the basis of this criterion, about 2% to 3% of these patients who received 1,000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated BUN levels.

A limited number of paediatric AIDS patients have been treated with clarithromycin suspension for mycobacterial infections. The most frequently reported adverse events, excluding those due to the patient's concurrent condition, were tinnitus, deafness, vomiting, nausea, abdominal pain, purpuric rash, pancreatitis and increased amylase. Evaluations of laboratory values for these patients were made by analyzing those values outside the seriously abnormal level (i.e. the extreme

high or low limit) for the specified test. Based on these criteria, one paediatric AIDS patient receiving < 15 mg/kg/day of clarithromycin had a seriously abnormal (elevated) total bilirubin; of the patients receiving 15 to < 25 mg/kg/day of clarithromycin, there was one each reported as seriously abnormal SGPT, BUN and seriously decreased platelet count. None of these seriously abnormal values for these laboratory parameters were reported for patients receiving the highest dosage (> 25 mg/kg/day) of clarithromycin.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested eight grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed medicine and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Macrolides, ATC code: J01FA09

Clarithromycin is a semi-synthetic macrolide antibiotic obtained by substitution of the hydroxyl group in position 6 by a CH₃O group in the erythromycin lactonic ring. Specifically, clarithromycin is 6-O-Methyl Erythromycin A. The white to off-white antibiotic powder is bitter, practically odourless, essentially insoluble in water, and slightly soluble in ethanol, methanol, and acetonitrile. Its molecular weight is 747.96.

Microbiology

Clarithromycin is a macrolide antibiotic. Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunits of susceptible bacteria and suppresses protein synthesis.

Clarithromycin has demonstrated excellent *in vitro* activity against both standard strains of bacteria and clinical isolates. It is highly potent against a wide variety of aerobic and anaerobic Gram-positive and Gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally one log₂ dilution

more potent than the MICs of erythromycin. *In vitro* data also indicate clarithromycin has excellent activity against *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Helicobacter (Campylobacter) pylori*. *In vitro* and *in vivo* data show that this antibiotic has activity against clinically significant mycobacterial species.

The *in vitro* data indicate *Enterobacteriaceae*, pseudomonas species and other non-lactose fermenting Gram-negative bacilli are not sensitive to clarithromycin.

Clarithromycin is bactericidal to *Helicobacter pylori*, with activity greater at neutral pH than at acid pH.

Clarithromycin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in section 4.1.

Aerobic Gram-Positive microorganisms

Staphylococcus aureus

Streptococcus pneumoniae

Streptococcus pyogenes

Listeria monocytogenes

Aerobic Gram-negative microorganisms

Haemophilus influenzae

Haemophilus parainfluenzae

Moraxella catarrhalis

Neisseria gonorrhoeae

Legionella pneumophila

Other microorganisms

Mycoplasma pneumoniae

Chlamydia pneumoniae

(TWAR)

Mycobacteria

Mycobacterium leprae

Mycobacterium kansasii

Mycobacterium chelonae

Mycobacterium fortuitum

Mycobacterium avium complex (MAC) consisting of: Mycobacterium avium

Mycobacterium intracellulare

Beta-lactamase production should have no effect on clarithromycin activity.

NOTE: Most strains of methicillin-resistant and oxacillin-resistant staphylococci are resistant to clarithromycin.

Helicobacter

Helicobacter pylori

In cultures performed prior to therapy, *H. pylori* was isolated and clarithromycin MIC's were determined pre-treatment in 104 patients. Of these, four patients had resistant strains, two patients had strains with intermediate susceptibility, and 98 patients had susceptible strains.

The following *in vitro* data are available, but their clinical significance is unknown. Clarithromycin exhibits *in vitro* activity against most strains of the following microorganisms; however, the safety and effectiveness of clarithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive microorganisms

Streptococcus agalactiae

Streptococci (Group C, F, G) *Viridans group streptococci*

Aerobic Gram-negative microorganisms

Bordetella pertussis

Pasteurella multocida

Anaerobic Gram-positive microorganisms

Clostridium perfringens

Peptococcus niger

Propionibacterium acnes

Anaerobic Gram-negative microorganisms

Bacteroides melaninogenicus

Spirochetes

Borrelia burgdorferi

Treponema pallidum

Campylobacter

Campylobacter jejuni

The principal metabolite of clarithromycin in man and other primates is a microbiologically-active metabolite, 14-OH clarithromycin. This metabolite is as active or 1 to 2 fold less active than the parent compound for most organisms,

except for *H. influenzae* against which it is twice as active. The parent compound and the 14-OH-metabolite exert either an additive or synergistic effect on *H. influenzae in vitro* and *in vivo*, depending on bacterial strains.

Clarithromycin was found to be 2 to 10 times more active than erythromycin in several experimental animal infection models. It was shown, for example, to be more effective than erythromycin in mouse systemic infection, mouse subcutaneous abscess, and mouse respiratory tract infections caused by *S. pneumoniae*, *S. aureus*, *S. pyogenes*, and *H. influenzae*. In guinea pigs with Legionella infection this effect was more pronounced; an intraperitoneal dose of 1.6 mg/kg/day of clarithromycin was more effective than 50 mg/kg/day of erythromycin.

Susceptibility test

Quantitative methods that require measurement of zone diameters give the most precise estimates of susceptibility of bacteria to antimicrobial agents. One recommended procedure uses discs impregnated with 15 mcg of clarithromycin for testing susceptibility (Kirby-Bauer diffusion test); interpretations correlate inhibition zone diameters of this disc test with MIC values for clarithromycin. The MIC's are determined by the broth or agar dilution method. The recommended test medium for susceptibility testing of *Haemophilus influenzae* according to the National Committee of Clinical Laboratory Standards (NCCLS) is the Haemophilus Test Medium (H.T.M.).

The correlation of disc inhibition zone diameters with MIC's is given in Table 4:

Table 4: CLARITHROMYCIN INTERPRETIVE STANDARDS

Organisms	Inhibition Zone Diameter (mm)			MIC (mcg /mL)		
	S	I	R	S	I	R
All Organisms (except Haemophilus and Staphylococci)	≥ 18	14-17	≤13	≤ 1	2-4	≥ 8
Staphylococci	≥ 20	-	≤ 19	≤ 0.5	-	≥ 1
Haemophilus influenzae when tested on HTM*	≥ 13	11-12	≤ 10	≤ 8	16	≥ 32

*HTM = Haemophilus Test Medium S=susceptible I=intermediate R=resistant

With these procedures, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infective organism is not likely to respond to therapy. A report of "Intermediate Susceptibility" suggests the therapeutic effect of the medicine may be equivocal or that the organism would be susceptible if higher doses were used (intermediate susceptibility also referred to as moderately susceptible).

Clinical efficacy and safety

H. pylori is strongly associated with peptic ulcer disease. 90 to 100% of patients with duodenal ulcer and 70 to 80% of patients with gastric ulcer are infected with this pathogen. Eradication of *H. pylori* has been shown to reduce the rate of duodenal ulcer recurrence, thereby reducing the need for maintenance anti-secretory therapy.

Triple Therapy

In a well-controlled double blind study, *H. pylori* infected duodenal ulcer patients received triple therapy with clarithromycin 500 mg b.i.d, amoxicillin 1000 mg b.i.d and omeprazole 20 mg daily for 10 days or dual therapy with clarithromycin 500 mg t.i.d. and omeprazole 40 mg daily for 14 days.

H. pylori was eradicated in 90% of the patients receiving clarithromycin triple therapy and in 60% of the patients receiving dual therapy.

Dual Therapy

In well-controlled, double-blind studies, *H. pylori* infected duodenal ulcer patients received eradication therapy with clarithromycin 500 mg t.i.d. and omeprazole 40 mg daily for 14 days followed by omeprazole 40 mg (study A) or omeprazole 20 mg (studies B, C and D) daily for an additional 14 days; patients in each control group received omeprazole alone for 28 days.

In study A, *H. pylori* was eradicated in over 80% of patients who received clarithromycin and omeprazole, and in only 1% of patients receiving omeprazole alone. In studies B, C, and D, the combined eradication rate was over 70% in patients receiving clarithromycin and omeprazole, and less than 1% in patients receiving omeprazole alone. In each study, the rate of ulcer recurrence at 6 months was statistically lower in the clarithromycin and omeprazole treated patients when compared to patients receiving omeprazole alone.

Clarithromycin has been used in other treatment regimens for the eradication of *H. pylori* including: clarithromycin plus tinidazole and omeprazole or lansoprazole; clarithromycin plus metronidazole and omeprazole or lansoprazole; clarithromycin plus tetracycline, bismuth subsalicylate, and ranitidine; clarithromycin plus lansoprazole; and clarithromycin plus amoxicillin and lansoprazole.

5.2 Pharmacokinetics Properties

Absorption

Food intake immediately before dosing increases clarithromycin bioavailability by a mean of 25%. Overall, this increase is minor and should be of little clinical significance with the recommended dosing regimens. Clarithromycin may thus be administered in either the presence or absence of food.

Distribution, biotransformation and elimination

In vitro

In vitro studies showed that the protein binding of clarithromycin in human plasma averaged about 70% at concentrations of 0.45-4.5 mcg/mL. A decrease in binding to 41% at 45.0 mcg/mL suggested that the binding sites might become saturated, but this only occurred at concentrations far in excess of the therapeutic medicine levels.

In humans

Hepatic impairment

In a study comparing one group of healthy human subjects with a group of subjects with liver impairment who were given 250 mg of clarithromycin b.i.d. for two days and a single 250 mg dose the third day, steady state plasma levels and systemic clearing of clarithromycin were not significantly different between the two groups. In contrast, steady state concentrations of the 14-OH metabolite were markedly lower in the group of hepatic-impaired subjects. This decreased metabolic clearance of the parent compound by 14-hydroxylation was partially offset by an increase in the renal clearance of parent drug, resulting in comparable steady state levels of parent drug in the hepatic impaired and healthy subjects. These results indicate that no adjustment of dosage is necessary for subjects with moderate or severe hepatic impairment but with normal renal function.

Renal impairment

A study was conducted to evaluate and compare the pharmacokinetic profile of multiple 500 mg oral doses of clarithromycin in subjects with normal and decreased renal function. The plasma levels, half-life, C_{max} and C_{min} for both clarithromycin and its 14-OH metabolite were higher and AUC was larger in subjects with renal impairment. K_{elim} and urinary excretion were lower. The extent to which these parameters differed was correlated with the degree of renal impairment; the more severe the renal impairment, the more significant the difference (see section 4.2).

Elderly subjects

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

Concomitant omeprazole administration

A pharmacokinetic study was conducted with clarithromycin 500 mg t.i.d. and omeprazole 40 mg daily. When clarithromycin was given alone at 500 mg q 8h, the mean steady-state C_{max} value was approximately 3.8 mcg/mL and the mean C_{min} value was approximately 1.8 mcg/mL. The mean AUC_{0-8} for clarithromycin was 22.9 mcg.hr/mL. The T_{max} and half-life were 2.1 hr and 5.3 hr, respectively, when clarithromycin was dosed at 500 mg t.i.d.

In the same study when clarithromycin 500 mg t.i.d. was administered with omeprazole 40 mg daily, increases in omeprazole half-life and AUC_{0-24} were observed. For all subjects combined, the mean omeprazole AUC_{0-24} was 89% greater and the harmonic mean for omeprazole $t_{1/2}$ was 34% greater when omeprazole was administered with clarithromycin than when omeprazole was administered alone. When clarithromycin was administered with omeprazole, the steady state C_{max} , C_{min} , and AUC_{0-8} of clarithromycin were increased by 10%, 27%, and 15%, respectively, over values achieved when clarithromycin was administered with placebo.

At steady state, clarithromycin gastric mucus concentrations 6 hours post-dosing were approximately 25-fold higher in the clarithromycin/omeprazole group compared with the clarithromycin alone group. Six hours post-dosing, mean clarithromycin gastric tissue concentrations were approximately 2-fold higher when clarithromycin was given with omeprazole than when clarithromycin was given with placebo.

Mycobacterium avium infections

Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of usual doses to adult patients with HIV infection were similar to those observed in normal subjects. However, at the higher doses which may be required to treat mycobacterial infections, clarithromycin concentrations were much higher than those observed at the usual doses. In adult HIV-infected patients taking 2000 mg/day in two divided doses, steady-state clarithromycin C_{max} values ranged from 5-10 mcg/mL. C_{max} values as high as 27 mcg/mL have been observed in HIV-infected adult patients taking 4000 mg/day in two divided doses. Elimination half-lives appeared to be lengthened at these higher doses as compared to those seen with usual doses in normal subjects. The higher plasma concentrations and longer elimination half-lives observed at these doses are consistent with the known nonlinearity in clarithromycin pharmacokinetics.

5.3 Preclinical safety data

Acute, subchronic and chronic toxicity

Studies were conducted in mice, rats, dogs and/or monkeys with clarithromycin administered orally. The duration of administration ranged from a single oral dose to repeated daily oral administration for 6 consecutive months.

In acute mouse and rat studies, 1 rat, but no mice, died following a single gavage of 5 g/kg body weight. The median lethal dose, therefore, was greater than 5 g/kg, the highest feasible dose for administration.

No adverse effects were attributed to clarithromycin in primates exposed to 100 mg/kg/day for 14 consecutive days or to 35 mg/kg/day for 1 month. Similarly, no adverse effects were seen in rats exposed to 75 mg/kg/day for 1 month, to 35 mg/kg/day for 3 months, or to 8 mg/kg/day for 6 months. Dogs were more sensitive to clarithromycin, tolerating 50 mg/kg/day for 14 days, 10 mg/kg/day for 1 and 3 months, and 4 mg/kg/day for 6 months without adverse effects.

The major clinical signs at toxic doses in these studies described above included emesis, weakness, reduced food consumption and reduced weight gain, salivation, dehydration, and hyperactivity. Two of 10 monkeys receiving 400 mg/kg/day died on treatment day 8; yellow discoloured faeces were passed on a few isolated occasions by some surviving monkeys given a dose of 400 mg/kg/day for 28 days.

The primary target organ at toxic dosages in all species was the liver. The development of hepatotoxicity in all species was detectable by early elevation of serum concentrations of alkaline phosphatase, alanine and aspartate aminotransferase, gamma-glutamyl transferase, and/or lactic dehydrogenase. Discontinuation of the medicine generally resulted in a return to or toward normal concentrations of these specific parameters.

Additional tissues less commonly affected in the various studies included the stomach, thymus and other lymphoid tissues, and the kidneys. Conjunctival injection and lacrimation, following near therapeutic dosages, occurred in dogs only. At a massive dosage of 400 mg/kg/day, some dogs and monkeys developed corneal opacities and/or edema.

The intravenous LD50 of clarithromycin I.V. in mice was found to be 184 mg/kg and 227 mg/kg in two separate studies. This was several times higher than the LD50 in rats (64 mg base/kg). These values were lower than those obtained following administration to mice by other routes. Signs of toxicity in both species were decreased activity, ataxia, jerks, tremors, dyspnoea and convulsions.

Vein irritation

Solutions of clarithromycin I.V. were evaluated for potential to cause vein irritation in the marginal ear vein of rabbits. This study demonstrated that administration of single doses at very high concentrations (7.5 to 30 mg/base/mL) were mildly irritating.

Fertility, reproduction, mutagenicity and teratogenicity

Fertility and reproduction studies have shown daily dosages of 150 to 160 mg/kg/day (10 times the maximal human dose) to male and female rats caused no adverse effects on the oestrous cycle, fertility, parturition, and number and viability of offspring. Two teratogenicity studies in both Wistar (po) and Sprague-Dawley (po and i.v) rats, one study in New Zealand White rabbits and one study in cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin. Only in one

additional study in Sprague-Dawley rats at similar doses and essentially similar conditions did a very low, statistically insignificant incidence (approximately 6%) of cardiovascular anomalies occur. These anomalies appeared to be due to spontaneous expression of genetic changes within the colony. Two studies in mice also revealed a variable incidence of cleft palate (3 to 30%) following doses of 70 times the upper range of the usual daily human clinical dose (500 mg b.i.d), but not at 35 times the maximal daily human clinical dose, suggesting maternal and foetal toxicity but not teratogenicity.

Clarithromycin has been shown to produce embryonic loss in monkeys when administered at approximately 10 times the upper range of the usual daily human dose (500 mg b.i.d), starting at gestation day 20. This effect has been attributed to maternal toxicity of the medicine at very high doses. An additional study in pregnant monkeys at dosages of approximately 2.5 to 5 times the maximal intended daily dosage (500 mg b.i.d.) produced no unique hazard to the conceptus.

A dominant lethal test in mice given 1000 mg/kg/day (approximately 70 times the maximal human daily clinical dose) was clearly negative for any mutagenic activity, and, in a Segment I study of rats treated with up to 500 mg/kg/day (approximately 35 times the maximal daily human clinical dose) for 80 days, no evidence of functional impairment of male fertility due to this long-term exposure to these very high doses of clarithromycin was exhibited.

Studies to evaluate the mutagenic potential of clarithromycin were performed using both nonactivated and rat-liver-microsome-activated test systems (Ames Test). Results of these studies provided no evidence of mutagenic potential at medicine concentrations of 25 mcg/petri plate or less. At a concentration of 50 mcg the medicine was toxic for all strains tested.

Rats were administered 15, 50 and 160 mg base/kg/day of clarithromycin I.V. via tail vein. Significant signs of maternal toxicity were elicited at 160 mg/kg/day (reduced weight gain and reduced food consumption) and 50 mg/kg/day (reduced food consumption). Local effects of the test agent included swollen, bruised, necrotic and ultimate loss of a portion of the tail among high- dose animals. No effects on mean incidences of implantation sites or resorptions were noted. No visceral or skeletal abnormalities due to medicine administration were noted, except for the dose- related trend in the proportion of male foetuses with an undescended testis. Thus, despite significant maternal toxicity, manifested as vein irritation and reduced food consumption and weight gain, there was no evidence of embryotoxicity, embryoletality or teratogenicity at any doses.

Groups of mated rabbits were given clarithromycin I.V. at doses of 3, 10 and 30 mg base/kg/day. One dam treated at 3 mg/kg/day died on gestational day 29. Vein irritation was seen in control and all treatment groups. The incidence and severity of irritation were directly related to the concentration of the medicine in the formulation. Signs of maternal toxicity were elicited at 30 mg/kg/day (reduced weight gain and reduced food consumption). This incidence of abortion in the 30 mg/kg/day treatment group was significantly higher than that of the control group, but all aborted foetuses were found to be grossly normal. The no-effect levels for maternal and foetal toxicity were 10 and 30 mg/kg/day, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Iron oxide yellow
Macrogol
Titanium dioxide
Colloidal silicon dioxide
Croscarmellose sodium
Magnesium stearate
Microcrystalline cellulose

Apo-Clarithromycin is:
Gluten Free
Lactose Free

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

24 months from the date of manufacture.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

Apo-Clarithromycin 250 mg tablets packed in blisters are available in pack sizes of 2, 14, 28 and 100.

Apo-Clarithromycin 250 mg tablets packed in bottles are available in pack sizes of 14, 28 and 100.

Apo-Clarithromycin 500 mg tablets packed in blisters are available in pack sizes of 3, 14, 20, 28, 42 and 100.

Apo-Clarithromycin 500 mg tablets packed in bottles are available in pack sizes of 14, 20, 28, 42 and 100.

Not all strengths and pack sizes may be available

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Apotex NZ Ltd
32 Hillside Road
Wairau Valley
Private Bag 102-995
North Shore Mail Centre
Auckland
Telephone: (09) 444 2073
Fax: (09) 444 2951

9. DATE OF FIRST APPROVAL

11 March 2010

10. DATE OF REVISION OF THE TEXT

23 October 2018

Summary Table of Changes

Section changed	Summary of new information
Whole data sheet	Updated to SmPC-style format. Updated as per latest approved information.
4.4	Additional safety related data as per latest approved information.