AUSTRALIAN PRODUCT INFORMATION

KALIXOCIN®

Clarithromycin film coated tablets

1 NAME OF THE MEDICINE

Clarithromycin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

KALIXOCIN (clarithromycin) is a semi-synthetic macrolide antibiotic. Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol and acetonitrile and practically insoluble in water.

KALIXOCIN tablets contain sorbates. For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

The KALIXOCIN 250 mg tablet is yellow, oval and film-coated, containing 250 mg clarithromycin.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

KALIXOCIN (clarithromycin) is indicated for use in adults and children older than 12 years for the treatment of mild to moderately severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

1. Acute streptococcal pharyngitis;

2. Community acquired pneumonia due to *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Streptococcus pneumoniae* (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE regarding sensitivity testing);

3. Uncomplicated skin and skin structure infections due to *Staphylococcus aureus* or *Streptococcus pyogenes* (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE regarding sensitivity testing);

4. Disseminated or localised mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare* and skin and skin structure infections due to *Mycobacterium chelonae*. Clarithromycin should be used in combination with other antimycobacterial agents;

5. Prevention of disseminated *Mycobacterium avium* complex infection in HIV-infected adults with CD4 lymphocyte counts <75 cells/mm^3 (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Disseminated infection due to *Mycobacterium avium* complex should be excluded by a negative blood culture prior to commencement of prophylaxis;

6. Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*;

7. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

KALIXOCIN (clarithromycin) is indicated for use in children for the treatment of mild to moderately severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

1. Acute streptococcal pharyngitis and tonsillitis caused by *Streptococcus pyogenes*;

2. Community acquired pneumonia including infections due to *Chlamydia pneumoniae, Mycoplasma pneumoniae* and *Legionella pneumophila*;

3. Skin and skin structure infections (e.g. impetigo);

4. Disseminated or localised infections due to *Mycobacterium avium* or *Mycobacterium intracellulare* in immunocompromised children, including those with HIV Infection or AIDS;

5. Acute otitis media.

NOTE:

1. Penicillins are the drug of first choice in the treatment of acute otitis media.

2. Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections including prophylaxis of rheumatic fever. Clarithromycin appears to be as effective as phenoxymethylpenicillin in the eradication of streptococci from the nasopharynx, however substantial data establishing the efficacy of clarithromycin in the subsequent prevention of rheumatic fever are not available at present.

3. There is insufficient evidence of efficacy to support the use of KALIXOCIN in acute bronchitis in young children.

4. The data presented on infections of skin and skin structure were confined largely to mild to moderate infections such as impetigo.

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Patients with Non-Mycobacterial Infections

The usual recommended dosage of clarithromycin in adults and children 12 years of age and older, is 250 mg twice daily. In more severe infections, the dosage can be increased to 500 mg twice daily. The usual duration of therapy is 7 to 14 days.

For the treatment of *Legionella pneumophila* infection, a dose of 500 mg twice daily for 4 weeks is appropriate.

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. Treatment should not be continued beyond 14 days in these patients.

NOTE: In the treatment of haemolytic streptococcal infections, a therapeutic regimen should be administered for at least 10 days.

Patients with Peptic Ulcers

In patients with peptic ulcer due to *H. pylori* infection, clarithromycin can be administered in a dose of 500 mg twice daily in combination with other appropriate antimicrobial treatments and a proton pump inhibitor for 7-14 days in consultation with national or international guideline recommendations for *H. pylori* eradication.

Patients should be treated again if there is a return of symptoms and *H. pylori* infection. However, in this situation, possible resistance of the organism to the antimicrobial agents should be considered.

The optimal treatment regimen for the eradication of *H. pylori* is yet to be determined.

Patients with Mycobacterial Infections

A. Treatment of mycobacterial infections

The recommended dosage for adults and children 12 years and older with disseminated or localised mycobacterial infections is 500 mg twice daily.

Clarithromycin should be used in conjunction with other antimycobacterial agents; the optimal regimen for treating patients with mycobacterial infections is yet to be determined.

Treatment with clarithromycin should continue as long as clinical benefit is demonstrated.

Experience in patients older than 65 years is limited. The recommended starting dose for elderly patients with calculated creatinine clearance of greater than 30 mL/min is 500 mg twice a day. A further reduction of the initial dose and dose titration is recommended in those patients with possible severe renal impairment (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Paediatric Patients

The recommended dosage for children (< 12 years) with disseminated or local mycobacterial infections is 7.5 to 15 mg/kg twice daily, not exceeding a maximum dose of 500 mg twice daily.

B. Prophylaxis of mycobacterial infections

The recommended dosage of clarithromycin in HIV-infected adults with CD4 lymphocyte counts <75 cells/mm^3 for prophylaxis of disseminated *Mycobacterium avium* complex infections is 500 mg twice daily. Disseminated disease due to *Mycobacterium avium* complex should be excluded by a negative blood culture prior to commencement of prophylaxis, and concurrent medication reviewed to avoid the possibility of drug interaction. Should prophylaxis fail, at least two other non-macrolide agents with good antimycobacterial activity should be chosen empirically, as the isolate of *Mycobacterium avium* complex may be highly resistant to clarithromycin and other macrolides.

Clarithromycin has not been studied as a prophylactic agent in mycobacterial infections in other immunocompromised groups or in HIV-infected children. Also, clarithromycin has no useful activity against *Mycobacterium tuberculosis*.

4.3 CONTRAINDICATIONS

- Hypersensitivity to macrolide antibiotic drugs or any of its excipients.

- Concurrent administration of clarithromycin and any of the following drugs is contraindicated: astemizole, terfenadine, cisapride, domperidone, pimozide, as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.

- 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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

- Concomitant administration of clarithromycin and ergot alkaloids (e.g., ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

- Concomitant administration of clarithromycin and oral midazolam is contraindicated (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

- Concomitant administration of clarithromycin and lomitapide is contraindicated (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

- 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

- Clarithromycin (and other strong CYP3A4 inhibitors) should not be used concomitantly with colchicine (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

- Concomitant administration with ticagrelor or ranolazine is contraindicated.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

In vitro studies have demonstrated cross-resistance between clarithromycin, erythromycin, azithromycin and other macrolides, as well as lincomycin and clindamycin. Attention should be paid to this possibility when considering the use of clarithromycin.

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.

Cardiovascular Events

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides including clarithromycin (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Therefore, as the following situations may lead to an increased risk for ventricular arrhythmias (including torsades de pointes), clarithromycin should be used with caution in the following patients:

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

- Clarithromycin must not be given to patients with electrolyte disturbances such as hypomagnesaemia or hypokalaemia (see section 4.3 CONTRAINDICATIONS)

- Patients concomitantly taking other medicinal products associated with QT prolongation (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

- Concomitant administration of clarithromycin with astemizole, cisapride, domperidone, pimozide and terfenadine is contraindicated (see section 4.3 CONTRAINDICATIONS).

- Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3 CONTRAINDICATIONS).

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

Myasthenia Gravis

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

Pseudomembranous colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including macrolides. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range 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. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil), may prolong and/or worsen the condition and should not be used.

Prophylaxis of *Mycobacterium avium* complex infection

The majority of cases of disseminated *Mycobacterium avium* complex infection occur in patients with CD4 cell counts below 50 cells/mm^3. Some authorities recommend delay of initiation of prophylaxis until the cell count has fallen to 50 cells/mm^3.

Patients with duodenal ulcers

Patients with bleeding duodenal ulcers should be maintained on anti-secretory 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS: Colchicine). Concomitant administration of clarithromycin and colchicine is contraindicated. (see section 4.3 CONTRAINDICATIONS).

Triazolobenzodiazepines

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, intravenous or oromucosal midazolam (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS: Triazolobenzodiazepines).

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

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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

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.

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.

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

HMG-CoA Reductase Inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3 CONTRAINDICATIONS). 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.

Use in Hepatic Impairment

Clarithromycin is principally excreted via the liver and kidney. Clarithromycin is principally metabolised by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function.

Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment (see section 4.3 CONTRAINDICATIONS).

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.

Use in Renal Impairment

In the presence of significant renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate. Caution is advised in patients with moderate to severe renal insufficiency (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment (see section 4.3 CONTRAINDICATIONS).

Use in the Elderly

Dosage adjustments are recommended in those patients with possible severe renal impairment (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Paediatric Use

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

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Cisapride, Domperidone and Pimozide

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

Ergot alkaloids

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

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.

Terfenadine and astemizole

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 CONTRAINDICATIONS). 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 CONTRAINDICATIONS) 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, they 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.

Effects of Other Medicinal Products on Clarithromycin

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

Efavirenz, nevirapine, rifampicin, rifapentine and rifabutin

Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifapentine 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 of clarithromycin concentration (C_{min}) and AUC of 33% and 18%, respectively. Steady-state concentrations of 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 (99.8% decrease) of the formation of 14-OH-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} <30 mL/min the dose of clarithromycin

should be decreased by 75%. Doses of clarithromycin greater than 1 g/day should not be coadministered with ritonavir.

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

Conversely, clarithromycin increases ritonavir AUC by 12%; no dosage adjustment of ritonavir is recommended.

Fluoxetine

Fluoxetine is partially metabolised by the 2D6 isoform of P450. It is a weak inhibitor of CYP3A; theoretically, this inhibition could result in possible elevation of clarithromycin levels.

Effect of Clarithromycin on Other Medicinal Products

Antiarrhythmics

There have been post-marketed 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 drugs. 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 Hypoglycaemic Agents/Insulin

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

The following drugs or drug classes are known or suspected to be metabolised by the same CYP3A isoenzyme (not a comprehensive list): alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporin, disopyramide, domperidone, ergot alkaloids, ibrutinib, lomitapide, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, triazolam and vinblastine. Drugs interacting by similar mechanisms through other isozymes within the CYP450 system include phenytoin, theophylline and sodium valproate.

Direct acting oral anticoagulants (DOACs)

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

Omeprazole

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

Sildenafil, tadalafil and vardenafil

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

Theophylline

Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range. In two studies in which theophylline was administered with clarithromycin (a theophylline sustained-release formulation was dosed at either 6.5 mg/kg or 12 mg/kg together with 250 mg or 500 mg every 12 hours clarithromycin), the steady-state levels of C_{max}, C_{min} and the area under the serum concentration time curve (AUC) increased about 20%. Theophylline dosage may need to be reduced.

Carbamazepine

Single-dose administration of clarithromycin has been shown to result in increased concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered.

Tolterodine

The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metaboliser population.

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

Erythromycin has been reported to decrease the clearance of triazolam and midazolam, and thus may increase the pharmacologic effect of these benzodiazepines. 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 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 drug interactions and 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.

Repaglinide

Clarithromycin may enhance and/or prolong the hypoglycaemic effect of repaglinide. In an interaction study in healthy volunteers, co-administration of 250 mg clarithromycin, a mechanism-based inhibitor of CYP3A4,

increased the repaglinide AUC by 40% and C_{max} by 67%, and increased the mean incremental AUC of serum insulin by 51% and the maximum concentration by 61%. The exact mechanism of this interaction is not clear.

Other Drug Interactions

Aminoglycosides

Caution is advised regarding concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Colchicine

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

Digoxin

When clarithromycin and digoxin are administered together, inhibition of P-glycoprotein (P-gp) 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 and zidovudine in HIV infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can largely be avoided by staggering the doses of clarithromycin and zidovudine by at least two hours. This interaction does not appear to occur in paediatric HIV infected patients taking clarithromycin suspensions with zidovudine or didanosine.

Phenytoin and Sodium 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 sodium 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. 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 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. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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.

Interactions that have been investigated, for which outcome was negative

Didanosine

Simultaneous administration of clarithromycin tablets and didanosine in 12 HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.

Indinavir

The potential pharmacokinetic interaction between indinavir and clarithromycin was assessed in a 3-period, randomised, crossover, multiple-dose study. Plasma concentration profiles of indinavir were consistently slightly higher in the presence of clarithromycin, although C_{max} changed minimally. Thus, clarithromycin has a modest inhibitory effect on indinavir metabolism. Results suggest that indinavir competitively inhibits the oxidative metabolism of clarithromycin. The magnitude of the changes in the pharmacokinetics of clarithromycin and indinavir were not considered to be clinically significant, and co-administration of the drugs does not require dose-adjustment.

Ketoconazole

Ketoconazole appreciably inhibits the N-demethylation of erythromycin. At this time there is no data regarding concomitant administration of ketoconazole and clarithromycin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Studies in rats have not shown any evidence of effects on fertility or reproductive performance following daily oral dosing up to 150 mg/kg/day in females (1.4-fold the MRHD based on body surface area), and up to 500 mg/kg/day in males (5-fold the MRHD on a body surface area basis).

Use in Pregnancy: Category B3

Clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the foetus. Clarithromycin has demonstrated adverse effects on pregnancy outcome and /or embryo-foetal development in monkeys, rats, mice and rabbits at doses that produced plasma levels 2 to 17 times the serum levels achieved in humans treated at the maximum recommended doses.

Four teratogenicity studies in rats (3 with oral doses and one with intravenous doses up to 160 mg/kg/day administered during the period of organogenesis) and two in rabbits (at oral doses up to 125 mg/kg/day or intravenous doses of 160 mg/kg/day administered during gestation days 6 to 18) failed to demonstrate any teratogenicity due to clarithromycin. Two other studies in rats under similar conditions demonstrated a low

incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6 to 15. Plasma AUC values after administration of 150 mg/kg/day to rats were approximately comparable with AUC values in humans given 500 mg clarithromycin twice daily. Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day during gestation days 6 to 15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day dose in mice resulted in AUC values 9 times the AUC values in humans given 500 mg clarithromycin twice a day. Abortions were observed in monkeys receiving 150 mg/kg/day on days 20 to 50 of pregnancy. AUC values in monkeys receiving this dose were about 2.5-fold higher than AUC values in humans given 500 mg clarithromycin twice daily.

The safety of clarithromycin for use in pregnancy has not yet been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embryofoetal development cannot be excluded. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risks.

Use in Lactation

The safety of clarithromycin for use during breastfeeding of infants has not been established. Clarithromycin and other macrolides are excreted in 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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience

Non-Mycobacterial Infections

At the recommended doses for non-mycobacterial infections, clarithromycin was generally well tolerated in the reported clinical trials. The incidence of adverse reactions considered to be remotely, possibly or probably related to treatment was comparable in nature to that with other macrolide antibiotics. Most adverse reactions were described as mild to moderately severe; less than 1% were described as severe. Fewer than 3% of patients discontinued therapy because of drug related side effects. The following side effects have been reported as common (1-10%) and uncommon (0.1-1%).

Table 2. Adverse effects – clinical trial experience

Body System	**Clarithromycin 250 mg Tablets N=4532**
Body as a Whole	
Common	infection, asthenia
Uncommon	body aches and pains
Cardiovascular System	
Uncommon	chest pain
Central Nervous System	
Common	headache*, dizziness

Uncommon	depression, sleep disturbance, tremor, flushing
Eye Disorders	
Uncommon	photophobia
Digestive System	
Common	nausea*, vomiting*, abdominal pain*, diarrhoea*, constipation*
Uncommon	bleeding gums, heartburn, stomatitis, blood stained stools
Haematopoietic & Lymphatic System	
Uncommon	increased prothrombin time
Metabolic & Nutritional	
Common	increases in ALT, AST*
Uncommon	increases in LDH, alkaline phosphatase, bilirubin, urea nitrogen*
Musculoskeletal	
Uncommon	back pain
Skin and Skin Structure	
Common	pruritis*
Uncommon	pustular rash (non urticarial) stained finger nails
Special Senses	
Uncommon	dysgeusia

* See Immunocompromised and HIV/AIDS patients

Hepatic System

As with other macrolides, hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with and without jaundice, has been infrequently reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In very rare instances (0.03%), hepatic failure with fatal outcomes has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.

The following adverse events have not been reported in clinical trials with clarithromycin but have rarely been associated with erythromycin products - ventricular arrhythmias, including ventricular tachycardia and *torsades de pointes* in individuals with prolonged QT intervals.

Immunocompromised and HIV/AIDS 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 drug events by patients treated with total daily doses of 1000 mg of clarithromycin are reported in the table above.

Approximately 2% to 3% of these patients who received 1000 mg of clarithromycin daily had seriously abnormal elevated levels (greater than three times upper limit of normal) of aspartate transaminase (AST) and alanine transaminase (ALT) and abnormally low white blood cell (less than 2×10^9 /L) or platelet (less than

75 x 10^9 /L) counts. A lower percentage of patients in these two dosage groups also had elevated blood urea levels. Slightly higher incidences of abnormal laboratory values were also noted with these patients for all parameters except for white blood cell count (WBC).

Elderly Patients

Limited data is available in elderly patients with *Mycobacterium avium* complex infections. In a clinical study, 11/13 patients on doses of clarithromycin between 1000 mg and 2000 mg per day discontinued therapy due to adverse events

Other Reported Side Effects

In addition to hepatic dysfunction, side effects such as pseudomembranous colitis, pancreatitis, thrombocytopenia, and a reduction in prothrombin time have also been reported with the use of clarithromycin.

Post-Marketing Experience

Adverse events have been reported during post-approval use of clarithromycin. Because these events 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 clarithromycin exposure.

Table 3. Adverse effects – post-marketing experience

Body System	Adverse Reaction
Body as a Whole	anaphylaxis abdominal pain asthenia hypersensitivity fever headache angioedema chills fatigue
Skin and Skin Structure	Severe cutaneous adverse reactions (SCAR) (e.g. acute generalised exanthematous pustulosis (AGEP) Steven-Johnson Syndrome urticaria rash hyperhidrosis pruritus toxic epidermal necrolysis drug rash with eosinophilia and systemic symptoms (DRESS) acne Henoch-Schonlein purpura
Central Nervous System	anxiety insomnia* somnolence hallucinations confusion psychotic disorder vertigo

	dizziness dream abnormality tinnitus disorientation depersonalisation nervousness hyperkinesia depression paraesthesia mania There have been rare reports of convulsions.
Haematopoietic & Lymphatic System	decreased white blood cell counts decreased platelet counts thrombocytopenia thrombocythemia leukopenia agranulocytosis
Metabolic & Nutritional	increased serum creatinine increased gamma glutamyl transferase (GGT) hypoglycaemia[1] anorexia decreased appetite
Special Senses	dysgeusia hearing disturbances taste perversion parosmia (smell perversion) ageusia anosmia otitis media deafness
Digestive System	dry mouth tongue discolouration glossitis stomatitis diarrhoea nausea vomiting liver abnormalities tooth discolouration dyspepsia enteritis abdominal distension eructation flatulence gastritis

	There have been rare reports of pancreatitis.
Respiratory System	dyspnoea
Urogenital System	dysuria renal failure Isolated cases of increased serum creatinine have been reported but an association has not been established. There have been reports of interstitial nephritis coincident with clarithromycin use.
Cardiac System[2]	torsades de pointes electrocardiogram QT prolonged ventricular tachycardia ventricular fibrillation palpitations
Hepatobiliary System[3]	hepatic failure hepatitis hepatitis cholestatic jaundice cholestatic jaundice hepatocellular cholestasis hepatic function abnormal
Musculoskeletal and Connective Tissue Disorders[4]	myalgia rhabdomyolysis myopathy muscle spasms
Infections and Infestations	pseudomembranous colitis erysipelas erythrasma candidiasis vaginal infection
Vascular Disorders	haemorrhage
Investigations	International Normalised Ratio (INR) increased prothrombin time prolonged urine colour abnormal

[1] There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin.

[2] As with other macrolides, QT prolongation, ventricular tachycardia and torsades de points have rarely been reported with clarithromycin.

[3] 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.

[4] 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).

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 INTERACTIONS WITH OTHER MEDICINES AND

OTHER FORMS OF INTERACTIONS - Colchicine and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

* See Immunocompromised and HIV/AIDS patients

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce pronounced gastrointestinal symptoms. Severe liver toxicity, including cholestatic jaundice may occur. One patient who had a history of bipolar disorder ingested eight grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxemia.

There is no known antidote. Treatment consists of prompt elimination of the unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunits of susceptible organisms and inhibiting protein synthesis.

Microbiology

The minimum inhibitory concentrations (MIC) of clarithromycin are generally one $\log_2$ dilution more potent than the MICs of erythromycin. However, clarithromycin is much more potent than erythromycin against atypical mycobacteria.

Clarithromycin is active in vitro and in vivo against the organisms listed below.

Table 3. In vitro and in vivo activity of clarithromycin

USUALLY SENSITIVE BACTERIA	NON-SENSITIVE BACTERIA
Chlamydia pneumoniae (TWAR)	*Enterobacteriaceae*
Haemophilus influenzae	*Pseudomonas* species
Haemophilus parainfluenzae	
Helicobacter pylori	
Legionella pneumophila	
Moraxella (Branhamella) catarrhalis	
Mycobacterium avium	
Mycobacterium chelonae	
Mycobacterium intracellulare	
Mycoplasma pneumoniae	
Staphylococcus aureus	

Streptococcus pneumoniae *Streptococcus pyogenes* A-haemolytic Streptococci (viridans group)	

Note:

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

2. Clarithromycin is not active in vitro against *M. tuberculosis*.

The principal metabolite of clarithromycin in man is a microbiologically active metabolite, 14-OH-clarithromycin. This metabolite is as active or one to two-fold less active than the parent compound for most organisms, except against *H. influenzae* where it is twice as active.

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 is more pronounced; an intraperitoneal dose of 1.6 mg/kg/day of clarithromycin was more effective than 50 mg/kg/day of erythromycin.

Susceptibility tests

Susceptibility Testing of Bacteria Other Than Atypical Mycobacteria

Dilution or Diffusion Techniques

Either quantitative (MIC) or breakpoint should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicated that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the results should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Susceptibility Testing of Atypical Mycobacteria

No standard reference method for susceptibility testing of atypical mycobacteria currently exists, nor has a correlation between the results of in vitro susceptibility testing and clinical efficacy been clearly established. Clinical isolates of M. avium and M. intracellulare resistant to clarithromycin have been reported. Susceptibility testing of atypical mycobacteria requires specialised techniques and media, and should be referred to a mycobacterial reference laboratory.

Clinical Trials

In a well-controlled, double-blind study, *H. pylori* infected duodenal ulcer patients received triple therapy with clarithromycin 500 mg twice a day, amoxicillin 1000 mg twice a day and omeprazole 20 mg daily for 10 days or dual therapy with clarithromycin 500 mg three times a day and omeprazole 40 mg daily for 14 days. *H. pylori* was eradicated in 88% of the patients (intent-to-treat analysis) receiving triple therapy and in 55% of the patients (intent-to-treat analysis) receiving dual therapy.

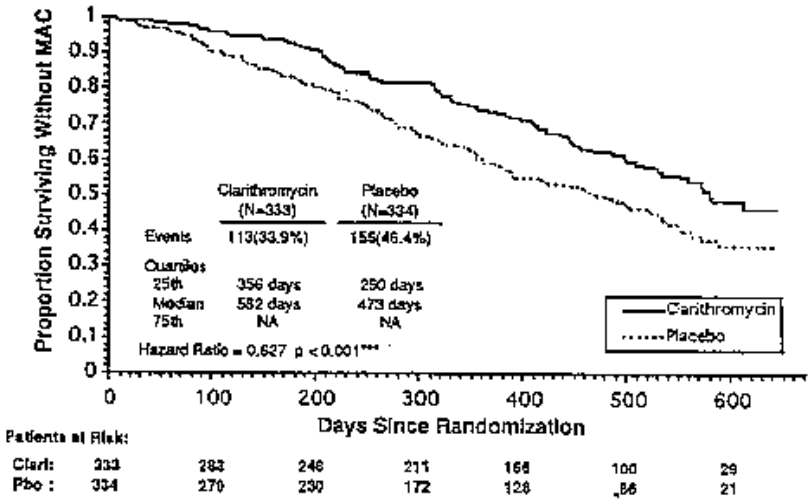
Helicobacter pylori is strongly associated with peptic ulcer disease. 90 to 100% of patients with peptic ulcers are infected with this pathogen. Eradication of *H. pylori* is associated with a reduction in the rate of duodenal ulcer recurrence, thereby reducing the need for maintenance anti-secretory therapy. The development of antimicrobial resistance may have an adverse effect on eradication regimens. The clinical impact of clarithromycin resistance on *H. pylori* eradication has not been studied. The optimal treatment regimen for the eradication of *H. pylori* is yet to be determined.

In a randomised, double-blind study of the safety and efficacy of clarithromycin for the prevention of disseminated *Mycobacterium avium* Complex (MAC) infection in HIV-infected patients with CD4 counts ≤ 100 cells/mm^3, 113 (33.9%) clarithromycin patients and 155 (46.4%) placebo patients either died or developed a MAC infection. This represents a statistically significant ($p<0.001$) reduction of 37% in the combined risk of developing MAC or dying for the clarithromycin group compared to the placebo group. The following figure summarises the analysis of MAC-free survival.

Figure 1. Analysis of MAC-free survival

MAC - Free Survival

All Randomised Patients



5.2 PHARMACOKINETIC PROPERTIES

Absorption

Clarithromycin is absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg tablets is approximately 50%. Two 250 mg clarithromycin tablets have been shown to be bioequivalent to one 500 mg tablet. The 250 mg/5 mL powder for oral liquid has been demonstrated to be bioequivalent to the 250 mg clarithromycin tablet.

Food intake half an hour before tablet dosing increased both the rate and extent of clarithromycin absorption, the effects being greater with the 500 mg tablet than with the 250 mg tablet. In a study on the 250 mg tablets, the mean C_{max} and AUC values were 0.72 ± 0.27 µg/mL and 4.3 ± 1.5 µg.h/mL (fasting) and 0.84 ± 0.38 µg/mL and 4.7 ± 1.7 µg.h/mL (non-fasting), respectively. In a study of the 500 mg tablets, the mean C_{max} and AUC values were 1.6 ± 0.6 µg/mL and 12.6 ± 4.0 µg.h/mL (fasting) and 2.5 ± 0.8 µg/mL and 15.7 ± 4.9 µg.h/mL (non-fasting) respectively. The consequences for the clinical efficacy of the increase in bioavailability caused by food are not known.

In a study of the powder for oral liquid in adults (250 mg dose), food was found to reduce the bioavailability of clarithromycin. AUC was reduced from 7.2 ± 2.5 to 6.5 ± 3.7 µg.h/mL and C_{max} was reduced from 1.24 ± 0.36 to 0.095 ± 0.44 µg/mL. T_{max} increased from 3.3 ± 1.2 to 5.3 ± 1.9 h.

In a pharmacokinetic study (7.5 mg/kg/day dose) in children with respiratory or skin infections, food was found to increase the C_{max} (3.59 ± 1.47 µg/mL (fasting) to 4.58 ± 2.76 µg/mL (non-fasting)) and AUC (10.0 ± 5.49 µg.h/mL (fasting) to 14.2 ± 9.39 µg.hr/mL.) The data are insufficient to allow any definitive statement regarding the timing of administration of clarithromycin powder for oral liquid with food.

In studies of fasting healthy adults, peak serum concentrations were attained within 2 hours after oral dosing. Steady-state peak serum clarithromycin concentrations were attained in 2 to 3 days and were approximately 1 µg/mL with a 250 mg dose administered every 12 hours and 2 to 3 µg/mL with a 500 mg dose administered every 12 hours. The elimination half-life of clarithromycin was about 3 to 4 hours with 250 mg administered every 12 hours but increased to 5 to 7 hours with 500 mg administered every 12 hours. The non-linearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 12 hours but is quite marked at higher doses. With a 250 mg every 12 hours dosing, the principal metabolite, 14-OH clarithromycin, attains a peak steady-state concentration of about 0.6 µg/mL and has an elimination half-life of 5 to 6 hours. With a 500 mg every 12 hours dosing, the peak steady-state concentrations of 14-OH clarithromycin are slightly higher (up to 1 µg/mL) and its elimination half-life is about 7 hours. With either dose, the steady-state concentration of this metabolite is generally attained within 2 to 3 days.

Distribution

Clarithromycin and the 14-OH clarithromycin metabolite distribute readily into body tissues and fluids. In vitro studies showed that protein binding of clarithromycin in human plasma averaged about 70% at clinically relevant concentrations of 0.45 to 4.5 mg/mL. Because of high intracellular concentrations, tissue concentrations may be higher than serum concentrations (See table). Animal studies indicate that clarithromycin penetration into the CNS is poor.

Table 4. Tissue and serum concentrations of clarithromycin

CONCENTRATION (after 250 mg every 12 h)		
Tissue Type	Tissue (µg/g)	Serum (µg/mL)
Tonsil	1.6	0.8
Lung	8.8	1.7

Information was obtained regarding the penetration of clarithromycin in middle ear fluid in paediatric patients with otitis media. Approximately 2.5 hours after receiving the fifth dose (dosage was 7.5 mg/kg twice a day) the mean concentration of clarithromycin was 2.53 µg/g fluid in the middle ear and for the 14-OH metabolite was 1.27 µg/g. The concentrations of parent drug and 14-OH metabolite were variable, with two thirds of patients having levels greater than corresponding concentration in serum and one third of patients having levels similar or lower. The mean ratio was 2.48 ± 3.57.

Metabolism

A number of drugs are metabolised by specific forms (isoforms) of the cytochrome-P450 enzyme system. If two drugs are metabolised by the same isoform, the propensity for an interaction between the two drugs is magnified.

Studies demonstrate that clarithromycin undergoes cytochrome-P450 dependent N-demethylation and 14-(R)-hydroxylation in the presence of human liver microsomes. Available data indicate that N-demethylation and 14-(R)-hydroxylation of clarithromycin are mediated principally by members of the CYP3A subfamily, most likely CYP3A4, and that CYP2C19, CYP2D6, CYP2E1, CYP1A2, CYP2C9 and CYP2A6 play relatively minor roles.

Excretion

Approximately 20% of a 250 mg oral dose given every 12 hours is excreted in the urine as unchanged clarithromycin. After a dose of 500 mg every 12 hours, urinary excretion of unchanged parent drug is approximately 30%. The renal clearance of clarithromycin is however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH-clarithromycin, which accounts for an additional 10% to 15% of either a 250 mg or 500 mg dose administered every 12 hours.

Pharmacokinetics in Special Populations

Impaired Hepatic Function: The steady-state concentrations of clarithromycin in patients with impaired hepatic function did not differ from those of normal patients; however, the 14-OH-clarithromycin concentrations were lower in the hepatically impaired patients. The decreased formation of 14-OH-clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the patients with impaired hepatic function when compared to healthy patients.

Impaired Renal Function: The pharmacokinetics of clarithromycin was also altered in patients with impaired renal function who received multiple 500 mg doses. The plasma levels, half-life, C_{max}, C_{min} for both clarithromycin and its 14-OH metabolite were higher and the AUC was larger in patients with renal impairment than in normal patients. 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. Plasma levels and elimination half-life start increasing at creatinine clearance values of less than 30 mL/min. The need for dosage adjustment should be considered in such cases (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Helicobacter pylori infection with concomitant omeprazole administration: A pharmacokinetic study was conducted with clarithromycin 500 mg three times a day and omeprazole 40 mg daily. When clarithromycin was given alone at 500 mg every eight hours, the mean steady-state C_{max} value was approximately 3.8 µg/mL and the mean C_{min} value was approximately 1.8 µg/mL. The mean AUC_{0-8} for clarithromycin was 22.9 µg·hr/mL. The T_{max} and half-life were 2.1 hr and 5.3 hr, respectively, when clarithromycin was dosed at 500 mg three times a day.

In the same study when clarithromycin 500 mg three times a day 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.

Mycobacterial infection: The steady-state concentrations of clarithromycin and 14-OH-clarithromycin in adults with HIV infection did not differ from those in non-HIV infected patients. 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 1000 mg/day in two divided doses, steady state clarithromycin C_{max} values ranged from 5 to 10 µg/mL. Elimination half-lives appeared to be lengthened at these higher doses as compared to that seen with usual doses in non-HIV infected patients. The higher plasma concentrations and longer elimination half-lives observed at these doses are consistent with the known non-linearity of clarithromycin pharmacokinetics.

5.3 PRECLINICAL SAFETY DATA

Hepatotoxicity, atrophy of lymphatic tissues (lymph, thymus) and adverse reproductive toxicity were seen in several species at exposures less than those which might be expected clinically at proposed doses. The clinical significance of these observations is not known.

Genotoxicity

Clarithromycin gave negative results in a battery of mutagenicity studies with the exception of a positive result in an in vitro chromosome aberration assay.

Carcinogenicity

Long-term studies in animals have not been performed to assess carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain the excipients: microcrystalline cellulose, croscarmellose sodium, hyprolose, hypromellose, magnesium stearate, povidone, propylene glycol, quinoline yellow, silicon dioxide, sorbic acid, sorbitan mono-oleate, pregelatinised maize starch, stearic acid, purified talc, titanium dioxide and vanillin.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in blister packs of 14 tablets. Packed in PVC/PVDC/Aluminium blister packs.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

Australian Register of Therapeutic Goods (ARTG)

AUST R 99707 – KALIXOCIN clarithromycin 250 mg tablet blister pack

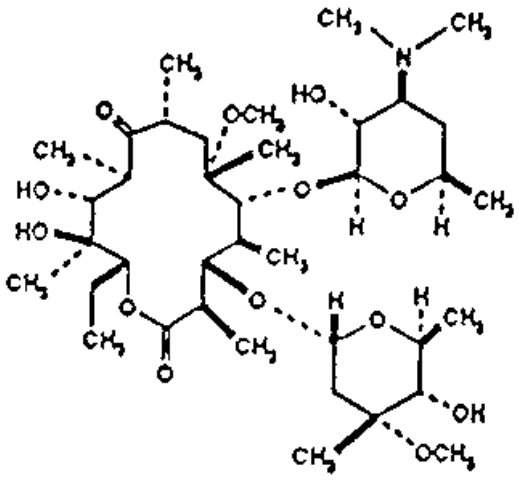
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemically, it is 6-0-Methyl Erythromycin A.

The molecular formula is $C_{38}H_{69}NO_{13}$, the molecular weight is 747.96 and the structural formula is:

Figure 2. Clarithromycin structural formula



CAS Number

81103-11-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

Australia

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

14/04/2004

10 DATE OF REVISION

06/05/2022

Summary Table of Changes

Section Changed	Summary of New Information
All	Editorial changes
4.2	Minor editorial update to the ‘Patient with peptic ulcers’ section
4.3	Added lomitapide as a contraindication Added hypomagnesaemia

4.4	Update to the cardiovascular events warning section Added the cautious use of clarithromycin with dabigatran, rivaroxaban and apixaban in patients with high bleeding risk Update to the 'Effects on laboratory tests' section
4.5	Update to the list of isozyme drug under CYP3A4-based interactions Added safety information on direct acting oral anticoagulants (DOACs)
4.6	Update to the 'Effects on fertility', 'Use in pregnancy' and 'Use in lactation' sections
4.8	Update to the 'Post-marketing experience' section - Table 3 Adverse effects – post-marketing experience Deleted clinical trial experience information in relation to immunocompromised and HIV/AIDS patients receiving higher than recommended doses of clarithromycin
5.1	Deleted clinical trial information relating to dual therapy regimen
6.5	Inserted AUST R numbers
8	Update sponsor's details

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