NEW ZEALAND DATA SHEET

KLACID®, KLACID® IV

1. Product Name

Klacid, 250 mg and 500 mg, film coated tablet.

Klacid, 250 mg/5 mL, granules for oral suspension.

Klacid IV, 500 mg, powder for injection.

2. Qualitative and Quantitative Composition

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

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

Klacid 250 mg/5 ml: Each 5 ml of the granules for suspension contains 250 mg of clarithromycin.

Klacid IV: Each vial contains 739.5 mg clarithromycin lactobionate, corresponding to 500 mg of clarithromycin.

For the full list of excipients, see section 6.1.

Klacid Suspension: Contains sugars and sorbates.

Klacid Tablet: Contains sorbates

3. Pharmaceutical Form

Klacid 250 mg – yellow, ovaloid, film coated tablets.

Klacid 500 mg – pale yellow, ovaloid, film coated tablets.

Klacid 250 mg/5 ml: white to off-white granules.

Klacid IV: white to off-white caked, lyophilized powder.

4. Clinical Particulars

4.1 Therapeutic indications

Klacid I.V. is indicated whenever parenteral therapy is required for treatment of sensitive microorganisms in the following conditions:

- Upper respiratory tract infections.
- Lower respiratory tract infections (see section 4.4 and 5.1 regarding Sensitivity testing).
- Skin and soft tissue infections (see section 4.4 and 5.1 regarding Sensitivity testing).

Klacid Suspension is indicated for treatment of infections caused by susceptible organisms. Such infections include:

- Upper respiratory infections (e.g. streptococcal pharyngitis).
- Lower respiratory infections (e.g. bronchitis, pneumonia) (see section 4.4 and 5.1 regarding Sensitivity testing).
- Acute otitis media.
- Skin and skin structure infections (e.g. impetigo, folliculitis, cellulitis, abscesses) (see section 4.4 and 5.1 regarding Sensitivity testing).
- Disseminated or localized mycobacterial infections due to *Mycobacterium avium or Mycobacterium intracellulare. Localised infections* due to *Mycobacterium chelonae, Mycobacterium fortuitum* or *Mycobacterium kansasii.*

Klacid 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

Klacid Tablet

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.

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 *Mycobacterium avium* complex (MAC) prophylaxis

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

Dosage for duodenal ulcer associated with *H. Pylori* Triple therapy regimen

The recommended dose of clarithromycin is 500mg twice daily in combination with other appropriate anti-microbial treatments and a proton pump inhibitor for 7-14 days in consultation with national or international guideline recommendations for *H.Pylori* eradication.

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 Klacid Tablets has not been studied in children less than 12 years of age. For children under 12 years of age Klacid Suspension should be used.

Klacid Suspension

Adults

Clarithromycin suspension may be used as an alternative dosage form for those adults that prefer a liquid medicine. The prepared suspension can be taken with or without meals, and can be taken with milk.

Special populations

Paediatric

Clinical trials have been conducted using clarithromycin pediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin pediatric suspension (granules for oral suspension).

The recommended daily dosage of clarithromycin suspensions in children is 7.5 mg/kg twice daily up to a maximum dose of 500 mg twice daily for non-mycobacterial infections. The usual duration of treatment is for 5 to 10 days depending on the pathogen involved and the severity of the condition. The prepared suspension can be taken with or without meals, and can be taken with milk.

Table 1 is a suggested guide for determining dosage.

Table 1: Suggested Guide for Determining Dosage

Based on Body Wt.	
Weight*	Dosage (7.5mg/kg) in mL given twice daily (250 mg/5 mL)
8-11 kg	1.25 mL
12-19 kg	2.5 mL
20-29 kg	3.75 mL
30-40 kg	5 mL
* Children < 8 kg should be dosed on a per kg basis (approx 7.5 mg/kg twice daily)	

Dosage in patients with mycobacterial infections

In children with disseminated or localized mycobacterial infections (*M. avium, M. intracellulare, M. chelonae, M. fortuitum, M. kansasii*), the recommended dose is 7.5 to 15 mg/kg clarithromycin twice daily, not exceeding a maximum dose of 500 mg twice daily.

Treatment of disseminated MAC infections in AIDS patients should be continued as long as clinical and microbiological benefit is demonstrated. Treatment of other mycobacterial infections should continue at the discretion of the physician. Clarithromycin should be used in conjunction with other antimycobacterial agents.

Dosage guidelines for paediatric patients with *Mycobacterial infections*

Table 2: Dosage Guidelines for Paediatric Patients with Mycobacterial infections		
Based on Body Weight		
Dosage in mL given twice daily (clarithromycin 250 mg/5 mL)		
Weight*	7.5 mg/kg bd	15 mg/kg bd
8-11 kg	1.25 mL	2.5 mL
12 - 19	2.5 mL	5 mL
20 - 29	3.75 mL	7.5 mL
30 - 40	5 mL	10 mL

* children < 8 kg should be dosed on a per kg basis (7.5 to 15 mg/kg twice daily).

Dosage in patients with renal impairment

In children with creatinine clearance less than 30 mL/min/1.73m^2, the dosage of clarithromycin should be reduced by one-half, i.e., up to 250 mg once daily, or 250 mg twice daily in more severe infections. Dosage should not be continued beyond 14 days in these patients.

Preparation for use

See section 6.6.

Klacid IV

The recommended dosage of clarithromycin I.V. in adults 18 years of age or older is 1 gram daily, divided into 2 equal doses, each infused, after further dilution with an appropriate I.V. diluent, over a 60-minute time period. At the present time, there are no data supporting intravenous use of clarithromycin in children.

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

Intravenous therapy may be limited for up to 2 to 5 days in the very ill patient and should be changed to oral therapy whenever possible as determined by the physician.

Dosage in patients with Mycobacterial infections

Although there currently is no data regarding use of clarithromycin I.V. in immunocompromised patients, data are available regarding the use of oral clarithromycin in HIV-infected patients. In disseminated or localized infections (*M. avium, M. intracellulare, M. chelonae, M. fortuitum, M. kansasii*), the recommended treatment, in adults, is 1000 mg/day in two divided doses.

Special populations

Renal impairment

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

Paediatric

There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age (see Klacid Suspension).

Preparation for use

See section 6.6.

4.3 Contraindications

- Hypersensitivity to macrolide antibiotics or any of the excipients listed in section 6.1. 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 sections 4.4 and 4.5).
- Concomitant administration of clarithromycin and ergot alkaloids (e.g., ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity (see section 4.5).
- Concomitant administration of clarithromycin and oral midazolam is contraindicated (see section 4.5).
- Concomitant administration of clarithromycin and lomitapide is contraindicated (see section 4.5).
- Clarithromycin must 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 and 4.5).
- Clarithromycin must not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia due to the risk of prolongation of the QT interval).
- Clarithromycin must not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
- Clarithromycin must 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) must not be used concomitantly with colchicine (see sections 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.

Renal impairment

Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.

Hepatic impairment

Clarithromycin is principally metabolized by the liver. Therefore, caution should be exercised in administering clarithromycin to patients with impaired hepatic function.

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.

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. *Clostridioides 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.

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).

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 is contraindicated in the following situations:

- Clarithromycin must not be given to patients with electrolyte disturbances such as hypomagnesaemia or hypokalaemia (see section 4.3).
- Concomitant administration of clarithromycin with astemizole, cisapride, domperidone, pimozide and terfenadine is contraindicated (see section 4.3).
- Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).

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 concomitantly taking other medicinal products associated with QT prolongation, other than those which are contraindicated (see section 4.5).

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.

Pneumonia

In view of the emerging resistance of *Streptococcus pneumoniae* to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia. In hospital-acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

Skin and soft tissue infections of mild to moderate severity

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

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g. acute generalized exanthematous pustulosis (AGEP), Stevens Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS)), clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Possible drug interactions

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.

HMG-CoA reductase inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3). Caution should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathy. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered (see section 4.5).

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.

Oral hypoglycemic agents/insulin

The concomitant use of clarithromycin and oral hypoglycemic agents (such as sulphonylureas) and/or insulin can result in significant hypoglycemia. Careful monitoring of glucose is recommended.

Oral anticoagulants

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

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

Myasthenia gravis

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

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.

Excipients

Clarithromycin Granules for Oral Suspension contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

When prescribing to diabetic patients, the sucrose content should be taken into account (see section 2).

4.5 Interaction 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, pimozide 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 pimozide concomitantly (see section 4.3).

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

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 (see section 4.3).

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, they should be administered in the lowest possible doses. 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, 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 and rifapentine

Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin and rifapentine may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14(R)-hydroxy-clarithromycin (14-OH-clarithromycin), a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

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 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 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 post marketing 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.

Hydroxychloroquine and chloroquine

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

Oral hypoglycemic 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 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, corticosteroids (e.g. methylprednisolone), cyclosporine, disopyramide, domperidone, ergot alkaloids, ibrutinib, ivabradine, lomitapide, lovastatin, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), 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.

Direct acting oral anticoagulants (DOACs)

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

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 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.

Triazolobenziodidiazepines (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. 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

Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of 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. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine to allow for a 4-hour interval between each medication. This interaction does not appear to occur in pediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and valproate

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

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.

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 (e.g., verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

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 twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in steady- state AUC and C_{max} values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two 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).

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. 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.

Breast-feeding

The safety of clarithromycin for use during breast-feeding of infants has not been established. Clarithromycin is excreted into human breast milk in small amounts. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin.

Fertility

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

4.7 Effects on ability to drive and use machines

There are no data on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

4.8 Undesirable effects

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

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 Klacid tablets, Klacid Once Daily, Klacid Suspension and Klacid IV.

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

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

Gastrointestinal disorders		Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain	Esophagitis, Gastrooesophageal reflux disease, gastritis, proctalgia, stomatitis, glossitis, abdominal distension, constipation, dry mouth, eructation, flatulence	Pancreatitis acute, tongue discolouration, tooth discolouration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis, hepatitis, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous, pruritus, urticaria, rash maculopapular	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
Musculoskeletal and connective tissue disorders			Muscle spasms, musculoskeletal stiffness[1], myalgia	Rhabdomyolysis**, myopathy
Renal and urinary disorders			Blood creatinine increased, blood urea increased	Renal failure, nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis[1]	Injection site pain[1], injection site inflammation[1]	Malaise, pyrexia, asthenia,chest pain, chills, fatigue	
Investigations			Albumin globulin ratio abnormal, blood alkaline phosphatase increased, blood lactate	International normalised ratio increased, prothrombin time prolonged, urine colour abnormal

			dehydrogenase increased	
*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. **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). [1] ADRs reported only for the Powder for Solution for Injection formulation				

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

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, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvate transaminase (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 Klacid Paediatric 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://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Symptoms

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.

Treatment

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.

In the case of overdosage, clarithromycin I.V. should be discontinued and all other appropriate supportive measures should be instituted.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use, macrolides, ATC code: J01FA09.

Microbiology

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 $\log_2$ dilution more potent than the MICs of erythromycin.

In vitro data also indicate clarithromycin has excellent activity against *Legionella pneumophila, Mycoplasma pneumoniae.* It is bactericidal to *Helicobacter pylori*; this activity of clarithromycin is greater at neutral pH than at acid pH. *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 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 gonorrheae
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 micrograms 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.

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

Klacid tablet

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 twice daily, amoxicillin 1000 mg twice daily and omeprazole 20 mg daily for 10 days or dual therapy with clarithromycin 500 mg three times daily 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.

Klacid suspension

Clinical experience in paediatric patients with non-mycobacterial infections

In clinical studies, clarithromycin at a dose of 7.5 mg/kg twice daily was demonstrated to be safe and effective in the treatment of paediatric patients with infections requiring oral antibiotic treatment. It has been evaluated in over 1200 children, ages six months to 12 years, with otitis media, pharyngitis, skin infections and lower respiratory tract infections.

In these studies, clarithromycin at a dose of 7.5 mg/kg twice daily. showed comparable clinical and bacteriological efficacy to the reference agents which included penicillin V, amoxicillin, amoxicillin/clavulanate, erythromycin ethylsuccinate, cefaclor and cefadroxil.

Clinical experience in paediatric patients with mycobacterial infections

A study in paediatric patients (some HIV positive) with mycobacterial infections demonstrated that clarithromycin was a safe and effective treatment when given alone and in combination with zidovudine or dideoxyinosine. Clarithromycin paediatric suspension was administered as 7.5, 15 or 30 mg/kg/day in two divided doses.

Some statistically significant effects on pharmacokinetic parameters were observed when clarithromycin was administered with antiretroviral compounds; however, these changes were minor and not likely to be of clinical significance. Clarithromycin at doses of up to 30 mg/kg/day was well-tolerated.

Clarithromycin was effective in the treatment of disseminated *M. avium* complex infections in paediatric patients with AIDS, with some patients demonstrating continued efficacy after more than one year of therapy.

5.2 Pharmacokinetic properties

Klacid Tablet

Absorption

The kinetics of orally administered clarithromycin has been studied extensively in a number of animal species and adult humans. These studies have shown clarithromycin is readily and rapidly absorbed with an absolute bioavailability of approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in any species following multiple dosing. 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 micrograms/mL. A decrease in binding to 41% at 45.0 micrograms/mL suggested that the binding sites might become saturated, but this only occurred at concentrations far in excess of the therapeutic medicine levels.

In vivo

Results of animal studies showed clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels. The highest concentrations were usually found in the liver and lung where the tissue to plasma (T/P) ratios reached 10 to 20.

Normal subjects

With twice daily dosing at 250 mg, the peak steady state plasma concentration was attained in 2 to 3 days and averaged about 1 micrograms/mL for clarithromycin and 0.6 micrograms/mL for 14-hydroxy- clarithromycin, while the elimination half-lives of the parent drug and metabolite were 3-4 hours and 5-6 hours, respectively. With twice daily dosing at 500 mg, the steady state C_{max} for clarithromycin and its hydroxylated metabolite were achieved by the fifth dose. After the fifth and seventh doses the C_{max} for clarithromycin averaged 2.7 and 2.9 micrograms/mL; and its hydroxylated metabolite averaged 0.88 and 0.83 micrograms/mL respectively. The half-life of the parent drug at the 500 mg dose level was 4.5 - 4.8 hours, while that of 14-hydroxy-clarithromycin was 6.9 - 8.7 hours. At steady state the 14-hydroxy-clarithromycin levels did not increase proportionately with the clarithromycin dose, and the apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at the higher doses. This non-linear pharmacokinetic behaviour of clarithromycin, coupled with the overall decrease in the formation of 14-hydroxylation and N-demethylation products at the higher doses, indicates that metabolism of clarithromycin approaches saturation at high doses.

In adults given single oral doses of 250 mg or 1200 mg clarithromycin, urinary excretion accounted for 37.9% of the lower dose and 46.0% of the higher dose. Faecal elimination accounted for 40.2%

and 29.1% (this included a subject with only one stool sample containing 14.1%) of these respective doses.

Patients

Clarithromycin and its 14-OH metabolite distribute readily into body tissues and fluids. Limited data from a small number of patients suggests clarithromycin does not achieve significant levels in cerebrospinal fluid after oral doses (i.e., only 1 to 2% of serum levels in CSF in patients with normal blood-CSF barriers). Concentrations in tissues are usually several fold higher than serum concentrations. Examples from tissue and serum concentrations are presented in Table 4 below.

Table 4: CONCENTRATION (after 250 mg every 12 hours)

Tissue Type	Tissue (micrograms/g)	Serum (micrograms/mL)
Tonsil	1.6	0.8
Lung	8.8	1.7

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 twice daily 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.

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 micrograms/mL. 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.

Concomitant omeprazole administration

A pharmacokinetic study was conducted with clarithromycin 500 mg three times daily and omeprazole 40 mg daily. When clarithromycin was given alone at 500 mg three times daily, the mean steady-state C_{max} value was approximately 3.8 micrograms/mL and the mean C_{min} value was approximately 1.8 micrograms/mL. The mean AUC_{0-8} for clarithromycin was 22.9 micrograms.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 daily.

In the same study when clarithromycin 500 mg three times daily 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.

<u>Klacid IV</u>

Distribution, biotransformation and elimination

Normal subjects

In a single-dose clinical study in volunteers, clarithromycin I.V. was administered at 75, 125, 250 or 500 mg doses in 100 mL volume infused over 30 minutes, and 500, 750 or 1,000 mg doses in 250 mL volume infused over a 60-minute period. The mean peak concentration (C_{max}) of parent drug ranged from 5.16 micrograms/mL after the 500 mg dose to 9.40 micrograms/ml after the 1000 mg dose (60 minute infusion).

The mean peak concentration (C_{max}) of the 14-hydroxy metabolite ranged from 0.66 micrograms/ml after the 500 mg dose to 1.06 micrograms/ml after the 1000 mg dose (60 minute infusion).

The mean terminal phase plasma half-life of parent drug was dose-dependent and ranged from 3.8 hours after the 500 mg dose to 4.5 hours after the 1000 mg dose (60 minute infusion). The mean estimated plasma half-life for the 14-hydroxy metabolite showed some dose-dependent increases at higher doses and ranged from 7.3 hours after the 500 mg dose to 9.3 hours after the 1000 mg dose (60 minute infusion). The mean area under the concentration vs. time curve (AUC) showed a nonlinear dose-dependent increase for parent drug of 22.29 h•micrograms/ml after the 500 mg dose to 53.26 h•micrograms /ml after the 1000 mg dose. The mean area under the concentration vs. time curve (AUC) for the 14-hydroxy metabolite ranged from 8.16 h•micrograms /ml after the 500 mg dose to 14.76 h•micrograms /ml after the1000 mg dose (60 minute infusion).

In a seven-day multiple dose clinical study subjects were infused with either 125 and 250 mg clarithromycin I.V. in 100 mL final volume over a 30 minute period or 500 and 750 mg of the formulation in final volumes of 250 mL over a 60-minute period; dosing was given at 12-hour intervals.

In this study, the observed mean steady-state peak clarithromycin (C_{max}) concentration increased from 5.5 micrograms/ml with the 500 mg dose to 8.6 micrograms/ml with the 750 mg dose. The mean apparent terminal half life was 5.3 hours after infusion of the 500 mg dose over a 60-minute period and 4.8 hours after a 60 minute infusion of 750 mg. The observed mean steady-state C_{max} for the 14-hydroxy metabolite increased from 1.02 micrograms/ml with the 500 mg dose to 1.37 micrograms/ml with the 750 mg dose. The mean terminal phase half-lives for this metabolite were

7.9 and 5.4 hours for the 500 and 750 mg dose groups, respectively. No dose-related trend was evident.

With twice daily oral dosing at 250 mg, the peak steady state plasma concentrations were attained in 2 to 3 days and averaged about 1 micrograms/mL for clarithromycin and 0.6 micrograms/mL for 14-hydroxy- clarithromycin, while the elimination half-lives of the parent drug and metabolite were 3-4 hours and 5-6 hours, respectively. With twice daily oral dosing at 500 mg, the steady state C_{max} for clarithromycin and its hydroxylated metabolite was achieved by the fifth dose. After the fifth and seventh doses, the steady state C_{max} for clarithromycin averaged 2.7 and 2.9 micrograms/mL; its hydroxylated metabolite averaged 0.88 and 0.83 micrograms/mL respectively.

The half-life of the parent drug at the 500 mg dose level was 4.5 - 4.8 hours, while that of the 14-hydroxy-clarithromycin was 6.9 - 8.7 hours. At steady state the 14-hydroxy-clarithromycin levels did not increase proportionately with the clarithromycin dose, and the apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at the higher doses. This non-linear pharmacokinetic behaviour of clarithromycin, coupled with the overall decrease in the formation of 14-hydroxylation and N-demethylation products at the higher doses, indicates that metabolism of clarithromycin approaches saturation at high doses.

The major metabolite in human plasma was the 14-OH-clarithromycin, with peak levels of 0.5 micrograms/mL and 1.2 micrograms/mL after doses of 250 mg and 1200 mg, respectively. In humans given single oral doses of 250 mg or 1200 mg clarithromycin, urinary excretion accounted for 37.9% of the lower dose and 46.0% of the higher dose. Faecal elimination accounted for 40.2% and 29.1% (this included a subject with only one stool sample containing 14.1%) of these respective doses.

Patients

Clarithromycin and its 14-OH metabolite distribute readily into body tissues and fluids. Examples from tissue and serum concentrations are presented below in Table 5:

Table 5: CONCENTRATION (after 250 mg every 12 hours)

Tissue Type	Tissue (micrograms/g)	Serum (micrograms/mL)
Tonsil	1.6	0.8
Lung	8.8	1.7

Patients with mycobacterial infections

Although summarized data are not currently available for the use of clarithromycin I.V. in mycobacterial infections, there are pharmacokinetic data from the use of clarithromycin tablets in these infections. Steady-state concentrations of clarithromycin and 14-OH-clarithromycin observed following administration of usual clarithromycin 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 usual doses. Elimination half-lives appeared to be lengthened at these higher doses, as compared to that seen with usual doses in normal subjects. The higher clarithromycin concentrations and longer elimination half-lives observed at these doses are consistent with the known nonlinearity in clarithromycin pharmacokinetics.

Klacid Suspension

Absorption

Initial pharmacokinetic data were obtained with clarithromycin tablet formulations. These data indicated the drug is rapidly absorbed from the gastrointestinal tract and the absolute bioavailability of clarithromycin 250 mg tablet was approximately 50%. Both the onset of absorption and the formation of the antimicrobially-active metabolite, 14-OH-clarithromycin, were slightly delayed by food, but the extent of bioavailability was not affected by administration of drug in the non-fasting state.

Distribution, biotransformation and elimination

In vitro

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 micrograms/mL.

Normal subjects

The bioavailability and pharmacokinetics of clarithromycin suspensions were investigated in adult subjects and in paediatric patients. A single-dose study in adult subjects found the overall bioavailability of the paediatric formulation to be equivalent to or slightly greater than that of the tablet (dosage with each was 250 mg). As with the tablet, administration of the paediatric formulation with food leads to a slight delay in the onset of absorption, but does not affect the overall bioavailability of clarithromycin. The comparative clarithromycin Cmax, AUC, and t½ for the paediatric formulation (non-fasted state) were 0.95 micrograms/mL, 6.5 micrograms hr/mL, and 3.7 hours, respectively, and for the 250 mg tablet (fasted state) were 1.10 micrograms/mL, 6.3 micrograms hr/mL, and 3.3 hours, respectively.

In a multiple dose study in which adult subjects were administered 250 mg of clarithromycin suspension every 12 hours, steady state blood levels were nearly reached by time of the fifth dose. Pharmacokinetic parameters after the fifth dose for clarithromycin suspension were: C_{max} 1.98 micrograms/mL, AUC 11.5 micrograms/mL, T_{max} 2.8 hours and t½ 3.2 hours for clarithromycin, and 0.67, 5.33, 2.9 and 4.9, respectively, for 14-OH-clarithromycin.

In fasting healthy human subjects, peak serum concentrations were attained within 2 hours after oral dosing. With twice daily dosing using a 50 mg tablet every 12 hours, steady-state peak serum concentrations or clarithromycin were attained in 2 to 3 days and were approximately 1 micrograms/mL. Corresponding peak serum concentrations were 2 to 3 micrograms/mL with a 500 mg dose administered every 12 hours.

The elimination half-life of clarithromycin was about 3 to 4 hours with a 250 mg tablet administered every 12 hours but increased to 5 to 7 hours with 500 mg administered every 12 hours. The principal metabolite, 14-OH-clarithromycin, attains a peak steady state concentration of about 0.6 micrograms/mL and has an elimination half-life of 5 to 6 hours after a dose of 250 mg every 12 hours. With a dose of 500 mg every 12 hours, the peak steady-state concentrations of 14-OH-clarithromycin are slightly higher (up to 1 micrograms/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.

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.

Patients

Clarithromycin and its 14-OH metabolite distribute readily into body tissues and fluids. Concentrations in tissues are usually several fold higher than serum concentrations. Examples from tissue and serum concentrations are presented below in Table 6:

Table 6: CONCENTRATION (after 250 mg every 12 hours)

Tissue Type	Tissue (micrograms/g)	Serum (micrograms/mL)

Tonsil	1.6	0.8
Lung	8.8	1.7

In pediatric patients requiring oral antibiotic treatment, clarithromycin demonstrated good bioavailability with a pharmacokinetic profile consistent with previous results from adult subjects using the same suspension formulation. The results indicated rapid and extensive drug absorption in children and, except for a slight delay in onset of absorption, food seemed to have no significant effect on drug bioavailability or pharmacokinetic profiles. Steady-state pharmacokinetic parameters obtained after the ninth dose on treatment day five were as follows for the parent drug: Cmax 4.60 micrograms/ml, AUC 15.7 micrograms/hr/ml and Tmax 2.8 hr; the corresponding values for the 14-OH metabolite were: 1.64 micrograms/ml, 6.69 micrograms/hr/ml, and 2.7 hr, respectively. Elimination half-life was estimated to be approximately 2.2 hr and 4.3 hr for the parent compound and metabolite, respectively.

In another study, information was obtained regarding the penetration of clarithromycin in middle ear fluid in patients with otitis media. Approximately 2.5 hours after receiving the fifth dose (dosage was 7.5 mg/kg twice daily), the mean concentration of clarithromycin was 2.53 micrograms/g fluid in the middle ear and for the 14-OH metabolite was 1.27 micrograms/g. The concentrations of parent drug and 14-OH metabolite were generally twice as high as the corresponding concentrations in serum.

Hepatic impairment

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

Renal impairment

The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function who received multiple 500 mg oral doses. The plasma levels, half-life, C_{max} and C_{min} for both clarithromycin and its 14-OH metabolite were higher and the AUC was larger in subjects with renal impairment than its normal subjects. 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

In a comparative study of healthy, young adults and healthy, elderly subjects given multiple 500 mg oral doses of clarithromycin, the circulating plasma levels were higher and elimination was slower in the elderly group compared to the younger group. However, there was no difference between the two groups when renal clearance of clarithromycin was correlated with creatinine clearance. It was concluded from these results that any effect on the handling of clarithromycin is related to renal function and not subject to age.

Patients with mycobacterial infections

Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of usual doses to patients with HIV infections (tablets for adults; granular suspension for children) were similar to those observed in normal subjects. However, at the higher doses which may be required to treat mycobacterial infections, clarithromycin concentrations can be much higher than those observed at usual doses.

In children with HIV infection taking 15-30 mg/kg/day of clarithromycin in two divided doses, steady-state C_{max} values generally ranged from 8 to 20 micrograms/mL. However, C_{max} values as high as 23 micrograms/mL have been observed in HIV-infected paediatric patients taking 30 mg/kg/day in two divided doses as clarithromycin paediatric suspension. Elimination half-lives appeared to be lengthened at these higher doses as compared to that observed 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

Klacid Tablet

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.

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 estrous 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 twice daily), 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 twice daily), 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 twice daily) 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.

Mutagenicity

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 micrograms/petri plate or less. At a concentration of 50 micrograms the medicine was toxic for all strains tested.

Klacid IV

Acute Toxicity

The intravenous LD_{50} 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 LD_{50} 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, dyspnea and convulsions.

Autopsy and histopathological examinations of survivors from the mouse study from which the LD_{50} of 184 mg/kg was obtained showed no changes associated with clarithromycin I.V. administration. However, in the other mouse and rat studies there were gross findings suggestive of pulmonary oedema together with patchy to diffuse dark-red discoloration of lung lobes in some animals that died acutely. Although administration of the drug produced similar effects in both mice and rats, it was much more toxic to rats than mice. The exact mode of toxicity could not be determined. Although the acute toxicity signs suggested central nervous system effect, the gross necropsies revealed pulmonary changes in some of the mice and rats.

The acute intravenous toxicities of several metabolites were evaluated in mice and are summarised below in Table 7:

Table 7: Intravenous toxicities in mice

Compound	$LD_{50\ (mg/kg)}$
Parent compound	184 and 227
M^1 metabolite (desmethyl)	200
M^4 metabolite (descladinosyl)	256
M^5 metabolite (isohydroxy)	337

Signs of toxicity included inhibition of movement, respiratory distress, and clonic convulsions. It is apparent that the toxicities of these metabolites are comparable to that of clarithromycin in both quality and degree.

Acute 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.

Subacute Toxicity

Subacute intravenous toxicity studies were performed over one month at dosage levels of 15, 50 and 160 mg/kg/day in rats and 5, 15, and 40 mg base/kg/day in monkeys. The top doses used in range-finding studies in rats (range 20 to 640 mg/kg/day) and monkeys (range 5 to 80 mg/kg/day) were found to be systemically toxic to the liver, biliary system and kidney. These are the same as the target organs found with studies in which clarithromycin was administered by the oral route.

The occurrence of severe vein irritation in the one-month studies in the rat and monkey at 160 mg/kg and 40 mg/kg, respectively, precluded the use of doses high enough to clearly demonstrate target organ toxicity. This occurred despite efforts to maximize dosing by increasing infusion volume and slowing the rate of infusion.

The no-effect-dosages in rats and monkeys determined by the one-month subacute studies were 50- and 15 mg/kg/day, respectively, and this was due to vein irritation at higher doses.

Embryotoxicity in Rats

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 drug administration were noted, except for from 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 reduced weight gain, there was no evidence of embryotoxicity, embryolethality or teratogenicity at any doses.

Embryotoxicity in Rabbits

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 drug in the formulation. Signs of maternal toxicity were elicited at 30 mg/kg/day (reduced weight gain and reduced food consumption). The 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.

Embryotoxicity in Monkeys

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

Mutagenicity

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 drug concentrations of 25 microgram/Petri plate or less. At a concentration of 50 microgram the drug was toxic for all strains tested.

Klacid Suspension

Acute and Subchronic Oral Toxicity Studies

The acute oral LD_{50} values for a clarithromycin suspension administered to three-day old mice were 1290 mg/kg for males and 1230 mg/kg for females. The LD_{50} values in three-day old rats were 1330 mg/kg for males and 1270 mg/kg for females. For comparison, the LD50 for orally-administered clarithromycin is about 2700 mg/kg for adult mice and about 3000 mg/kg for adult rats. These results are consistent with other antibiotics of the penicillin group, cephalosporin group and macrolide group in that the LD_{50} is generally lower in juvenile animals than in adults.

In both mice and rats, body weight was reduced or its increase suppressed and suckling behaviour and spontaneous movements were depressed for the first few days following drug administration. Necropsy of animals that died disclosed dark-reddish lungs in mice and about 25% of the rats; rats treated with 2197 mg/kg or more of a clarithromycin suspension were also noted to have a reddish-black substance in the intestines, probably because of bleeding. Deaths of these animals were considered due to debilitation resulting from the depressed suckling behaviour or bleeding from the intestines.

Pre-weaning rats (five days old) were administered a clarithromycin suspension formulation for two weeks at doses of 0, 15, 55, and 200 mg/kg/day. Animals from the 200 mg/kg/day group had decreased body-weight gains, decreased mean hemoglobin and hematocrit values, and increased mean relative kidney weights compared to animals from the control group. Treatment-related minimal to mild multifocal vacuolar degeneration of the intrahepatic bile duct epithelium and an increased incidence of nephritic lesions were also observed in animals from this treatment group. The "no-toxic effect" dosage for this study was 55 mg/kg/day.

An oral toxicity study was conducted in which immature rats were administered a clarithromycin suspension for six weeks at daily dosages of 0, 15, 50, and 150 mg base/kg/day. No deaths occurred and the only clinical sign observed was excessive salivation for some of the animals at the highest dosage from one to two hours after administration during the last three weeks of treatment. Rats from the 150 mg/kg dose group had lower mean body weights during the first three weeks, and were observed to have decreased mean serum albumin values and increased mean relative liver weight compared to the controls.

No treatment-related gross or microscopic histopathological changes were found. A dosage of 150 mg/kg/day produced slight toxicity in the treated rats and the "no effect dosage" was considered to be 50 mg/kg/day.

Juvenile beagle dogs, three weeks of age, were treated orally daily for four weeks with 0, 30, 100, or 300 mg/kg of clarithromycin, followed by a four-week recovery period. No deaths occurred and no changes in the general condition of the animals were observed. Necropsy revealed no abnormalities. Upon histological examination, fatty deposition of centrilobular hepatocytes and cell infiltration of portal areas were observed by light microscopy, and an increase in hepatocellular fat droplets was noted by electron microscopy in the 300 mg/kg dose group. The toxic dose in juvenile beagle dogs was considered to be greater than 300 mg/kg and the "no effect dose" 100 mg/kg.

Fertility, Reproduction, and Teratogenicity

Fertility and reproduction studies have shown daily dosages of 150 to 160 mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, and number and viability of offspring. Two teratogenicity studies in both Wistar (p.o.) and Sprague-Dawley (p.o. 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, twice daily.), 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 ten times the upper range of the usual daily human dose (500 mg twice daily.), starting at gestation day 20. This effect has been attributed to maternal toxicity of the drug at very high doses. An additional study in pregnant monkeys at dosages of approximately 2.5 to 5 times the maximal intended daily dosage of 500 mg twice daily. 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 of 500 mg twice daily) 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 of 500 mg twice daily) 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.

Mutagenicity

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 drug concentrations of 25 microgram/Petri plate or less. At a concentration of 50 microgram the drug was toxic for all strains tested.

6. Pharmaceutical Particulars

6.1 List of excipients

Klacid Tablets

Klacid tablets also contain:

- croscarmellose sodium,
- pregelatinized starch (250 mg tablet only),
- microcrystalline cellulose,
- povidone,
- silicon dioxide,
- hydroxypropylcellulose,
- talc,
- hypromellose,
- sorbitan monooleate,
- stearic acid,
- magnesium stearate,
- propylene glycol,
- sorbic acid
- vanillin flavour
- titanium dioxide (171)
- quinoline yellow (104)

Klacid Suspension

Klacid suspension consists of a granulation of clarithromycin and Carbopol which is coated with HP-55 polymer (hydroxypropyl methylcellulose phthalate).

Klacid suspension also contains:

- povidone,
- carbomer,
- hypromellose phthalate,
- castor oil,
- silicon dioxide,
- xanthan gum,
- potassium sorbate,
- citric acid,
- titanium dioxide,
- maltodextrin,
- sucrose
- fruit punch flavour.

Klacid suspension contains sulphites.

Klacid IV

Klacid IV also contains:
- lactobionic acid
- sodium hydroxide (for pH-adjustment).

6.2 Incompatibilities

No clinically relevant studies addressing physical compatibility of clarithromycin with other intravenous admixtures have been performed at this time.

Klacid IV must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Klacid Tablets

5 years

Klacid Suspension

250 mg/5 ml: 3.5 years (42 months)

After reconstitution, Klacid suspension should be stored at or below 30°C for no longer than 14 days. Do not refrigerate the reconstituted suspension but store at room temperature.

Klacid IV

3 years
After reconstitution, Klacid IV should be stored at 15 - 25°C for no longer than 24 hours.

6.4 Special precautions for storage

Klacid Tablets

Bottle: Store at or below 30°C.
Blister: Store below 25°C. Protect from light. Store in a dry place.

Klacid Suspension

250 mg/5ml: Store at or below 30°C in a well closed container.

For storage conditions after reconstitution of the medicine, see section 6.3.

Klacid IV

Store at or below 30°C.

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

Klacid Tablets

250 mg: PVC/PVDC blister. Pack-sizes of 10 or 14 tablets.

500 mg: PVC/PVDC blister. Pack-size of 10 or 14 tablets.

500 mg: HDPE bottle. Pack-size of 100 tablets.

Klacid Suspension

250 mg/5 ml: HDPE bottle with a polypropylene child resistant closure and polypropylene syringe. Pack-sizes of 50 ml or 100 ml.

Klacid IV

15 ml glass vial with a halobutyl lyophilisation stopper. Pack-size of 1 vial.

Not all dose forms or pack types and sizes may be marketed.

6.6 Special precautions for disposal and other handling

The final solution for infusion is prepared as follows:

1. Prepare the initial solution of clarithromycin I.V. by adding 10 mL of Sterile Water for Injection to the 500 mg vial. Use only Sterile Water for Injection, as other diluents may cause precipitation during reconstitution. Do not use diluents containing preservatives or inorganic salts.

Note: When the product is reconstituted as directed above, the resulting solution contains an effective antimicrobial preservative; each mL contains 50 mg of clarithromycin I.V. The reconstituted product should be used within 24 hours if stored at room temperature (25°C), or within 48 hours if stored at 5°C.

2. The reconstituted product (500 mg in 10 mL Water for Injection) should be added to a minimum of 250 mL of one of the following diluents before administration:

5% Dextrose in Lactated Ringer’s Solution, 5% Dextrose, Lactated Ringer’s, 5% Dextrose in 0.3% sodium chloride, Normosol-M in 5% Dextrose, Normosol-R in 5% Dextrose, 5% Dextrose in 0.45% sodium chloride, and 0.9% sodium chloride.
The final diluted product should be used within 6 hours if stored at room temperature (25° C), or within 48 hours if stored at 5° C.

No medicine or chemical agent should be added to a clarithromycin I.V. fluid admixture unless its effect on the chemical and physical stability of the solution has first been determined.

Klacid Suspension

Suspension 250 mg/5 mL

An appropriate amount of water (see paragraphs below) should be added to the powder in the bottle and shaken until all of the particles are suspended. Avoid vigorous and/or lengthy shaking. Shake prior to each subsequent use to ensure resuspension.

Add 27 mL of water to the granules in the 50 mL bottle to yield 50 mL of reconstituted suspension.

Add 52 mL of water to the granules in the 100 mL bottle to yield 100 mL of reconstituted suspension.

The concentration of each suspension will be 250 mg of clarithromycin per 5 mL and the suspension will have a shelf life of 14 days after reconstitution when stored at or below 30° C.

After reconstitution, Klacid suspension should be stored at or below 30°C for no longer than 14 days. Do not refrigerate the reconstituted suspension but store at room temperature.

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

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

Klacid Suspension & IV – 28 October 1993; Klacid Tablets – 16 April 1992

10. Date of Revision of the Text

15 March 2024

Section Changed	Summary of new information
All	Removed all reference to Klacid 125mg/5mL suspension as this strength is now lapsed.
4.3	Minor editorial changes to some of the contraindications.
4.4	Edoxaban added to paragraph on direct acting oral anticoagulants. Paragraph on 'Cardiovascular Events' re-structured to better differentiate between situations for contraindications and warnings.
4.5	Additional paragraph on interaction between clarithromycin and hydroxychloroquine/chloroquine and serious adverse cardiovascular events. Added corticosteroids and ivabradine to CYP3A-based interactions. Edoxaban added to paragraph on direct acting oral anticoagulants.
4.8	Updated ADR reporting URL.