PRODUCT INFORMATION

KLACID

NAME OF THE MEDICINE

Clarithromycin 250mg and 500mg Tablets
Clarithromycin 250mg/5mL Powder for Oral Liquid

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

The molecular formula is $\text{C}_{38}\text{H}_{69}\text{NO}_{13}$, the molecular weight is 747.96 and the structural formula is:

![Molecular Structure](image)

DESCRIPTION

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

The 250mg tablet is yellow, oval and film-coated, containing 250mg clarithromycin. The 500mg tablet is pale yellow, oval and film-coated, containing 500mg clarithromycin.

Klacid Powder for Oral Liquid consists of a granulation of clarithromycin and carbomer 934P and coated with HP-55 polymer (hypromellose phthalate). The 250mg/5mL suspension is fruit punch flavoured and sweetened with sucrose. Water is added to reconstitute the suspension prior to use. After mixing, each 5 mL contains 250mg of clarithromycin.

PHARMACOLOGY

Hepatotoxicity, atrophy of lymphatic tissues (lymph, thymus) and adverse reproductive toxicity were seen in several species at exposures less than those which might be expected clinically at
proposed doses. The clinical significance of these observations is not known. There are no data from long-term animal carcinogenicity studies.

**Clinical Pharmacokinetics**

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

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

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

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

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

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

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Tissue (µg/g)</th>
<th>Serum (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsil</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Lung</td>
<td>8.8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

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

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.

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

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

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

Impaired Renal Function: The pharmacokinetics of clarithromycin were also altered in patients with impaired renal function who received multiple 500 mg doses. The plasma levels, half-life, Cmax, Cmin for both clarithromycin and its 14-OH metabolite were higher and the AUC was larger in patients with renal impairment than in normal patients. The extent to which these parameters differed was correlated with the degree of renal impairment; the more severe the renal impairment, the more significant the difference. Plasma levels and elimination half-life start increasing at creatinine clearance values of less than 30 mL/min. The need for dosage adjustment should be considered in such cases (see DOSAGE AND ADMINISTRATION).
Helicobacter pylori infection with concomitant omeprazole administration: A pharmacokinetic study was conducted with clarithromycin 500 mg three times a day and omeprazole 40 mg daily. When clarithromycin was given alone at 500 mg every eight hours, the mean steady-state C_{max} value was approximately 3.8 µg/mL and the mean C_{min} value was approximately 1.8 µg/mL. The mean AUC_{0-8} for clarithromycin was 22.9 µg·hr/mL. The T_{max} and half-life were 2.1 hr and 5.3 hr, respectively, when clarithromycin was dosed at 500 mg three times a day.

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

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

Mycobacterial infection: The steady-state concentrations of clarithromycin and 14-OH-clarithromycin in adults with HIV infection did not differ from those in non-HIV infected patients. However, at the higher doses which may be required to treat mycobacterial infections, clarithromycin concentrations were much higher than those observed at the usual doses.

In adult HIV infected patients taking 1000 mg/day in two divided doses, steady state clarithromycin C_{max} values ranged from 5 to 10 µg/mL. Elimination half-lives appeared to be lengthened at these higher doses as compared to that seen with usual doses in non-HIV infected patients. The higher plasma concentrations and longer elimination half-lives observed at these doses are consistent with the known non-linearity of clarithromycin pharmacokinetics.

Clinical Pharmacology
Helicobacter pylori is strongly associated with peptic ulcer disease. Ninety to 100% of patients with peptic ulcers are infected with this pathogen. Eradication of H. pylori is associated with a reduction in the rate of duodenal ulcer recurrence, thereby reducing the need for maintenance anti-secretory therapy.

The development of antimicrobial resistance may have an adverse effect on eradication regimens. The clinical impact of clarithromycin resistance on H. pylori eradication has not been studied.

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

Microbiology
Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunits of susceptible organisms and inhibiting protein synthesis. The minimum inhibitory concentrations (MIC) of clarithromycin are generally one log2 dilution more potent than the MICs of
erythromycin. However, clarithromycin is much more potent than erythromycin against atypical mycobacteria.

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

<table>
<thead>
<tr>
<th>USUALLY SENSITIVE BACTERIA</th>
<th>NON-SENSITIVE BACTERIA</th>
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</thead>
<tbody>
<tr>
<td>Chlamydia pneumoniae (TWAR)</td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Pseudomonas species</td>
</tr>
<tr>
<td>Haemophilus parainfluenzae</td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td></td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td></td>
</tr>
<tr>
<td>Moraxella (Branhamella) catarrhalis</td>
<td></td>
</tr>
<tr>
<td>Mycobacterium avium</td>
<td></td>
</tr>
<tr>
<td>Mycobacterium chelonae</td>
<td></td>
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<tr>
<td>Mycobacterium intracellular</td>
<td></td>
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<tr>
<td>Mycoplasma pneumoniae</td>
<td></td>
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<tr>
<td>Staphylococcus aureus</td>
<td></td>
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<tr>
<td>Streptococcus pneumoniae</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td></td>
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<tr>
<td>α-haemolytic Streptococci (viridans group)</td>
<td></td>
</tr>
</tbody>
</table>

Note:
1. Most strains of methicillin-resistant and oxacillin-resistant staphylococci are resistant to clarithromycin.
2. Clarithromycin is not active in vitro against M. tuberculosis.

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

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

**Susceptibility Testing of Bacteria Other Than Atypical Mycobacteria:**

**Dilution or Diffusion Techniques**

Either quantitative (MIC) or breakpoint should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.
A report of “Susceptible” indicated that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the results should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

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

**Susceptibility Testing of Atypical Mycobacteria:**

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

**CLINICAL TRIALS**

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

In well controlled, double blind studies, *H. pylori* infected duodenal ulcer patients received eradication therapy with clarithromycin 500 mg tid and omeperazole 40mg daily for 14 days, followed by omeprazole 40 mg (study A) or omeprazole 20 mg (study B, C, D) daily for an additional 14 days. Patients in each control group received omeprazole alone for 28 days. In study A, *H. pylori* was eradicated in 81% of patients (intent-to-treat analysis), who received clarithromycin and omeprazole and in only 1% in patients receiving omeprazole alone. In studies B, C, and D, the combined eradication rate was from 56 to 68% (intent-to-treat analysis), in patients receiving clarithromycin and omeprazole and less than 1% in patients receiving omeprazole alone. The rate of ulcer recurrence at 6 months was statistically lower in the clarithromycin and omeprazole treated patients when compared to patients receiving omeprazole alone.

The development of antimicrobial resistance may have an adverse effect on eradication regimens. The clinical impact of clarithromycin resistance on *H. pylori* eradication has not been studied.

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

MAC - Free Survival
All Randomised Patients

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**INDICATIONS**

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

1. Acute streptococcal pharyngitis;
2. Community acquired pneumonia due to *Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila* and *Streptococcus pneumoniae*;
3. Uncomplicated skin and skin structure infections due to *Staphylococcus aureus* or *Streptococcus pyogenes*;
4. Disseminated or localised mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare* and skin and skin structure infections due to *Mycobacterium chelonae*. Clarithromycin should be used in combination with other antimycobacterial agents.
5. Prevention of disseminated *Mycobacterium avium* complex infection in HIV-infected adults with CD4 lymphocyte counts <75 cells/mm$^3$ (See PRECAUTIONS). Disseminated infection due to *Mycobacterium avium* complex should be excluded by a negative blood culture prior to commencement of prophylaxis.
6. Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae, Moraxella catarrhalis* or *Streptococcus pneumoniae*;
7. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

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

1. Acute streptococcal pharyngitis and tonsillitis caused by *Streptococcus pyogenes*;
2. Community acquired pneumonia including infections due to *Chlamydia pneumoniae, Mycoplasma pneumoniae* and *Legionella pneumophila*;
3. Skin and skin structure infections (eg impetigo);
4. Disseminated or localised infections due to *Mycobacterium avium* or *Mycobacterium intracellulare* in immunocompromised children, including those with HIV Infection or AIDS.
5. Acute otitis media.

NOTE:
1. Penicillins are the drug of first choice in the treatment of acute otitis media.
2. Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections including prophylaxis of rheumatic fever. Clarithromycin appears to be as effective as phenoxymethylpenicillin in the eradication of streptococci from the nasopharynx, however substantial data establishing the efficacy of clarithromycin in the subsequent prevention of rheumatic fever are not available at present.
3. There is insufficient evidence of efficacy to support the use of Klacid in acute bronchitis in young children.
4. The data presented on infections of skin and skin structure were confined largely to mild to moderate infections such as impetigo.

**CONTRAINDICATIONS**

Clarithromycin is contraindicated in patients with known hypersensitivity to macrolide antibiotic drugs or any of its excipients.

Concurrent administration of clarithromycin and any of the following drugs is contraindicated: astemizole, terfenadine, cisapride, pimozide, as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated, as this may result in ergot toxicity. Concomitant administration of clarithromycin with lovastatin or simvastatin is also contraindicated (see PRECAUTIONS).

Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointes (see PRECAUTIONS).
Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a p-glycoprotein inhibitor or a strong CYP3A4 inhibitor.

**PRECAUTIONS**

**General:** Clarithromycin is principally excreted via the liver and kidney. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of significant renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate. (See **DOSAGE AND ADMINISTRATION**). Caution is advised in patients with severe renal insufficiency.

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.

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

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

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

Due to the risk for QT prolongation clarithromycin should be used with caution in patients with a medical condition associated with an increased tendency toward QT prolongation and torsades de pointes.

**Myasthenia Gravis**

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

**Pseudomembranous colitis**

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

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

**Patients with duodenal ulcers**
Patients with bleeding duodenal ulcers should be maintained on anti-secretory therapy.

**Colchicine**
There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients. (See **Interactions with other Medicines: Colchicine**).

**Triazolobenzodiazepines**
Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and midazolam (see **Interactions with other Medicines: Triazolobenzodiazepines**).

**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 and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens Johnson Syndrome, toxic epidermal necrolysis, DRESS, and Henoch-Schönlein purpura clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see **Interactions with other Medicines**).

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

**Oral Anticoagulants**

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

**HMG-CoA Reductase Inhibitors**

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated and treatment with these agents should be discontinued during clarithromycin treatment (see CONTRAINDICATIONS). As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors. Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly. Patients should be monitored for signs and symptoms of myopathy.

Rare reports of rhabdomyolysis have also been reported in patients taking atorvastatin or rosuvastatin concomitantly with clarithromycin. When used with clarithromycin, atorvastatin or rosuvastatin should be administered in the lowest possible doses. Adjustment of the statin dose or use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin or pravastatin) should be considered.

**Use in pregnancy:** Category B3

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

Four teratogenicity studies in rats (3 with oral doses and one with intravenous doses up to 160 mg/kg/day administered during the period of organogenesis) and two in rabbits (at oral doses up to 125 mg/kg/day or intravenous doses of 160 mg/kg/day administered during gestation days 6 to 18) failed to demonstrate any teratogenicity due to clarithromycin. Two other studies in rats under similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6 to 15. Plasma AUC values after administration of 150 mg/kg/day to rats were approximately comparable with AUC values in humans given 500 mg clarithromycin twice daily. Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day during gestation days 6 to 15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day dose in mice resulted in AUC values 9 times the AUC values in humans given 500 mg clarithromycin twice a day. Abortions were observed in monkeys receiving 150 mg/kg/day on days 20 to 50 of pregnancy. AUC values in monkeys receiving this dose were about 2.5 fold higher than AUC values in humans given 500 mg clarithromycin twice daily.

The safety of clarithromycin for use in pregnancy has not yet been established. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.
Use in lactation
Clarithromycin and other macrolides are excreted in human breast milk. The safety of clarithromycin for use during breast-feeding of infants has not been established.

Use in the elderly
Dosage adjustments are recommended in those patients with possible severe renal impairment (See DOSAGE AND ADMINISTRATION).

Paediatric patients
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 Powder for Oral Liquid should be used.

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

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

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.

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

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

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

Terfenadine
Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes (see CONTRAINDICATIONS)
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 inhibitor administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

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

Etravirine
Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC.

Fluconazole
Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy adult volunteers led to increases in the mean steady-state of clarithromycin concentration (C_{min}) and AUC of 33% and 18%, respectively. Steady-state concentrations of 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir
A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg q 8 hours and clarithromycin 500 mg q 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin C_{max} increased by 31%, C_{min} increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition (99.8% decrease) of the formation of 14-OH-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CLCR 30 to 60mL/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 g/day should not be coadministered with ritonavir.

Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see section below, Bi-directional Drug Interactions).
Conversely, clarithromycin increases ritonavir AUC by 12%; no dosage adjustment of ritonavir is recommended.

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

Effect of Clarithromycin on Other Medicinal Products

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

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

As with other macrolide antibiotics, the use of clarithromycin in patients concurrently taking drugs metabolised by the cytochrome P450 system (e.g. alprazolam, cilostazol, oral anticoagulants such as warfarin, ergot alkaloids, methylprednisolone, quinidine, triazolam, valproate, vinblastine, midazolam, disopyramide, phenytoin, digoxin, tacrolimis, cyclosporin rifabutin and sildenafil) may be associated with elevations in serum levels of these other drugs.

Omeprazole
Clarithromycin (500mg every 8 hours) was given in combination with omeprazole (40mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (Cmax, AUC0-24 and t1/2 increased by 30%, 89% and 34% respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with clarithromycin.

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

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

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

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

Triazolobenzodiazepines (eg.triazolam and alprazolam) and related benzodiazepines (eg. midazolam):
Erythromycin has been reported to decrease the clearance of triazolam and midazolam, and thus may increase the pharmacologic effect of these benzodiazepines. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment.

The same precautions should also apply to other benzodiazepines 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 postmarketing reports of drug interactions and CNS effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Repaglinide
Clarithromycin may enhance and/or prolong the hypoglycaemic effect of repaglinide. In an interaction study in healthy volunteers, co-administration of 250mg clarithromycin, a mechanism based inhibitor of CYP3A4, increased the repaglinide AUC by 40% and Cmax by 67%, and increased the mean incremental AUC of serum insulin by 51% and the maximum concentration by 61%. The exact mechanism of this interaction is not clear.

**Other Drug Interactions**

Colchicine
Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by
clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity (see PRECAUTIONS).

Digoxin
When clarithromycin and digoxin are administered together, inhibition of P-glycoprotein (Pgp) by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentration should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine
Simultaneous oral administration of clarithromycin and zidovudine in HIV infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can largely be avoided by staggering the doses of clarithromycin and zidovudine by at least two hours. This interaction does not appear to occur in paediatric HIV infected patients taking clarithromycin suspensions with zidovudine or didanosine.

Phenytoin and 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 Drug Interactions

Atazanavir
Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance <30mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

Itraconazole
Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bi-directional drug interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir
Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see PRECAUTIONS, Drug Interactions).
Verapamil
Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

**Interaction that has been investigated, for which outcome was negative:**

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

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

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

**ADVERSE EFFECTS**

**Clinical Trial Experience**

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Klacid 250mg Tablets N=4532</th>
<th>Klacid 500mg Tablets N=658</th>
<th>Klacid Powder for Oral Liquid N= 1285</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>infection, asthenia</td>
<td>fever</td>
<td>infection, headache, fever</td>
</tr>
<tr>
<td>Uncommon</td>
<td>body aches and pains</td>
<td></td>
<td>moniliasis, accidental injury, flu syndrome</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>chest pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body System</td>
<td>Klacid 250mg Tablets</td>
<td>Klacid 500mg Tablets</td>
<td>Klacid Powder for Oral Liquid</td>
</tr>
<tr>
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<td>-----------------------------</td>
</tr>
<tr>
<td></td>
<td>N=4532</td>
<td>N=658</td>
<td>N= 1285</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>headache*, dizziness</td>
<td>headache</td>
<td>headache</td>
</tr>
<tr>
<td>Uncommon</td>
<td>depression, sleep disturbance, tremor, flushing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td></td>
<td>conjunctivitis</td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
<td></td>
<td>photophobia</td>
</tr>
<tr>
<td>Digestive System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>nausea*, vomiting*, abdominal pain*, diarrhoea*, constipation*</td>
<td>nausea*, vomiting*, abdominal pain*</td>
<td>diarrhoea, vomiting, abdominal pain</td>
</tr>
<tr>
<td>Uncommon</td>
<td>bleeding gums, heartburn, stomatitis, blood stained stools</td>
<td>flatulence*, dyspepsia</td>
<td>nausea, dyspepsia</td>
</tr>
<tr>
<td>Haematopoietic &amp; Lymphatic System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic &amp; Nutritional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>increases in ALT, AST*</td>
<td>increases in ALT,AST*, alkaline phosphatase</td>
<td>Increased in AST</td>
</tr>
<tr>
<td>Uncommon</td>
<td>increases in LDH, alkaline phosphatase, bilirubin, urea nitrogen*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>backpain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>dyspnoea*</td>
<td></td>
<td>rhinitis, increased cough, pharyngitis, asthma</td>
</tr>
<tr>
<td>Skin and Skin Structure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>pruritus</td>
<td>rash*</td>
<td>rash</td>
</tr>
<tr>
<td>Uncommon</td>
<td>pustular rash (non urticarial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special Senses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>taste perversion</td>
<td>taste perversion*</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

In adult patients, the most frequently reported adverse drug events by patients treated with total daily doses of 1000 mg - 2000 mg of clarithromycin are reported in the table above. The incidence is generally 3 - 4 times more frequent for those patients treated with total daily doses of 4000 mg of clarithromycin.
Approximately 2% to 3% of these patients who received 1000 mg or 2000 mg of clarithromycin daily had seriously abnormal elevated levels (greater than three times upper limit of normal) of aspartate transaminase (AST) and alanine transaminase (ALT) and abnormally low white blood cell (less than 2 x 10^9 /L) or platelet (less than 75 x 10^9 /L) counts. A lower percentage of patients in these two dosage groups also had elevated blood urea levels. Slightly higher incidences of abnormal laboratory values were also noted with these patients for all parameters except for white blood cell count (WBC).

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

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

**Post-Marketing Experience**
Adverse events have been reported during post-approval use of clarithromycin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to clarithromycin exposure.
<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td>anaphylaxis&lt;br&gt;abdominal pain&lt;br&gt;asthenia&lt;br&gt;allergic reaction&lt;br&gt;fever&lt;br&gt;headache</td>
</tr>
<tr>
<td><strong>Skin and Skin Structure</strong></td>
<td>Steven-Johnson Syndrome&lt;br&gt;urticaria&lt;br&gt;rash&lt;br&gt;pruritus&lt;br&gt;toxic epidermal necrolysis&lt;br&gt;drug rash with eosinophilia and systemic symptoms (DRESS)&lt;br&gt;acne&lt;br&gt;Henoch-Schonlein purpura</td>
</tr>
<tr>
<td><strong>Central Nervous System</strong></td>
<td>anxiety&lt;br&gt;insomnia*&lt;br&gt;hallucinations&lt;br&gt;confusion&lt;br&gt;psychosis&lt;br&gt;vertigo&lt;br&gt;dizziness&lt;br&gt;dream abnormality&lt;br&gt;tinnitus&lt;br&gt;disorientation&lt;br&gt;depersonalisation&lt;br&gt;dream abnormality&lt;br&gt;confusion&lt;br&gt;nervousness&lt;br&gt;hyperkinesia&lt;br&gt;depression.&lt;br&gt;There have been rare reports of convulsions.</td>
</tr>
<tr>
<td><strong>Haematopoietic &amp; Lymphatic system</strong></td>
<td>decreased white blood cell counts&lt;br&gt;decreased platelet counts&lt;br&gt;thrombocytopenia&lt;br&gt;leukopenia&lt;br&gt;agranulocytosis</td>
</tr>
<tr>
<td><strong>Metabolic &amp; Nutritional</strong></td>
<td>increased serum creatinine&lt;br&gt;increased gamma glutaryl transferase (GGT)&lt;br&gt;hypoglycaemia¹</td>
</tr>
<tr>
<td><strong>Special Senses</strong></td>
<td>hearing disturbances&lt;br&gt;taste perversion&lt;br&gt;smell perversion&lt;br&gt;ageusia&lt;br&gt;anosmia otitis media</td>
</tr>
<tr>
<td>Body System</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td>dry mouth</td>
</tr>
<tr>
<td></td>
<td>tongue discolouration</td>
</tr>
<tr>
<td></td>
<td>glossitis</td>
</tr>
<tr>
<td></td>
<td>moniliasis oral</td>
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<tr>
<td></td>
<td>stomatitis</td>
</tr>
<tr>
<td></td>
<td>diarrhoea</td>
</tr>
<tr>
<td></td>
<td>nausea</td>
</tr>
<tr>
<td></td>
<td>vomiting</td>
</tr>
<tr>
<td></td>
<td>liver abnormalities</td>
</tr>
<tr>
<td></td>
<td>tooth discolouration</td>
</tr>
<tr>
<td></td>
<td>dyspepsia, enteritis</td>
</tr>
<tr>
<td></td>
<td>There have been rare reports of pancreatitis.</td>
</tr>
<tr>
<td><strong>Respiratory System</strong></td>
<td>dyspnoea</td>
</tr>
<tr>
<td><strong>Urogenital System</strong></td>
<td>dysuria</td>
</tr>
<tr>
<td></td>
<td>renal failure</td>
</tr>
<tr>
<td></td>
<td>Isolated cases of increased serum creatinine have</td>
</tr>
<tr>
<td></td>
<td>been reported but an association has not been</td>
</tr>
<tr>
<td></td>
<td>established. There have been reports of interstitial</td>
</tr>
<tr>
<td></td>
<td>nephritis coincident with clarithromycin use.</td>
</tr>
<tr>
<td><strong>Cardiac System</strong></td>
<td>torsade de pointes</td>
</tr>
<tr>
<td></td>
<td>electrocardiogram QT prolonged</td>
</tr>
<tr>
<td></td>
<td>ventricular tachycardia</td>
</tr>
<tr>
<td><strong>Hepatobiliary System</strong></td>
<td>hepatic failure</td>
</tr>
<tr>
<td></td>
<td>hepatitis</td>
</tr>
<tr>
<td></td>
<td>hepatitis cholestatic</td>
</tr>
<tr>
<td></td>
<td>jaundice cholestatic</td>
</tr>
<tr>
<td></td>
<td>jaundice hepatocellular</td>
</tr>
<tr>
<td></td>
<td>hepatic function abnormal</td>
</tr>
<tr>
<td>**Musculoskeletal and Connective</td>
<td>myalgia</td>
</tr>
<tr>
<td>Tissue Disorders**</td>
<td>rabdomyolysis</td>
</tr>
<tr>
<td></td>
<td>myopathy</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>pseudomembranous colitis</td>
</tr>
<tr>
<td></td>
<td>erysipelas</td>
</tr>
<tr>
<td></td>
<td>erythrasma</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>haemorrhage</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>International Normalised Ratio (INR) increased</td>
</tr>
<tr>
<td></td>
<td>prothrombin time prolonged</td>
</tr>
<tr>
<td></td>
<td>urine colour abnormal</td>
</tr>
</tbody>
</table>

1. There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin.
2. As with other macrolides, QT prolongation, ventricular tachycardia and torsades de points have rarely been reported with clarithromycin.
3. In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.
4. In some reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients.
with renal insufficiency. Deaths have been reported in some such patients. (See Interactions with Other Medicines: Colchicine and PRECAUTIONS).

* See Immunocompromised and HIV/AIDS patients

DOSAGE AND ADMINISTRATION

Patients with nonmycobacterial infections
The usual recommended dosage of is 250 mg twice daily. In more severe infections, the dosage can be increased to 500 mg twice daily. The usual duration of therapy is 7 to 14 days.

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

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.

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

Paediatric patients
The recommended daily dosage of Klacid Powder for Oral Liquid in children is 7.5 mg/kg twice a day up to a maximum dose of 500 mg twice a day. There is insufficient data to allow any statement regarding the timing of administration of Klacid Powder for Oral Liquid with food. The usual duration of treatment is 5 to 10 days depending on the pathogen involved and the severity of the condition. Treatment for streptococcal pharyngitis should be 10 days.

The following table is a suggested guide for determining dosage:

<table>
<thead>
<tr>
<th>Klacid Paediatric Dosage in Children</th>
<th>Based on Body Weight in kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight*</td>
<td>250 mg/5 mL</td>
</tr>
<tr>
<td>8-11 kg (1-2 yrs)**</td>
<td>1.25mL</td>
</tr>
<tr>
<td>12-19 kg (2-4 yrs)</td>
<td>2.5mL</td>
</tr>
<tr>
<td>20-29 kg (4-8 yrs)</td>
<td>3.75mL</td>
</tr>
<tr>
<td>30-40 kg (8-12 yrs)</td>
<td>5mL</td>
</tr>
</tbody>
</table>

* children <8 kg should be dosed on a per kg basis (approx. 7.5 mg/kg/ BD)
** approximate ages

In children with creatinine clearance less than 30 mL/min, 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.
Patients With Peptic Ulcers
For the eradication of *H. pylori*, the recommended dosage regimen is clarithromycin 500 mg BD in conjunction with amoxycillin 1000 mg BD and omeprazole 20 mg twice daily for 7 - 10 days.

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

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

Patients With Mycobacterial Infections

A. Treatment of mycobacterial infections
The recommended dosage for adults and children older than 12 years with disseminated or localised mycobacterial infections is 500 mg twice daily. This may be increased to 1000 mg twice daily if no clinical or bacteriological response is seen after 3-4 weeks of therapy.

The recommended dosage for children (< 12 years) with disseminated or local mycobacterial infections is 15 - 30 mg/kg per day in 2 divided doses.

Experience in patients older than 65 years is limited. The recommended starting dose for elderly patients with calculated creatinine clearance of greater than 30 mL/min is 500 mg twice a day. A further reduction of the initial dose and dose titration is recommended in those patients with possible severe renal impairment. (See Precautions and Adverse Reactions)

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

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

B. Prophylaxis of mycobacterial infections
The recommended dosage of clarithromycin in HIV-infected adults with CD4 lymphocyte counts <75 cells/mm³ for prophylaxis of disseminated *Mycobacterium avium* complex infections is 500 mg twice daily. Disseminated disease due to *Mycobacterium avium* complex should be excluded by a negative blood culture prior to commencement of prophylaxis, and concurrent medication reviewed to avoid the possibility of drug interaction. Should prophylaxis fail, at least two other nonmacrolide agents with good antimycobacterial activity should be chosen empirically, as the isolate of *Mycobacterium avium* complex may be highly resistant to clarithromycin and other macrolides.

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

250mg/5 mL Powder for Suspension
Add 27mL of water to the powder in the 50mL bottle and shake to yield a reconstituted suspension containing 250mg/5mL.

Add 36mL of water to the powder in the 70mL bottle and shake to yield a reconstituted suspension containing 250mg/5mL.

Add 52mL of water to the powder in the 100mL bottle and shake to yield a reconstituted suspension containing 250mg/5mL.

OVERDOSAGE

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce pronounced gastrointestinal symptoms. Severe liver toxicity, including cholestatic jaundice may occur.

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

For advice on the management of overdose please contact the Poisons Information Centre. In Australia please call 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

KLACID 250mg tablets: Bottles of 2*, 100 tablets, Blister packs of 2*, 14 or 28* tablets.
KLACID 500mg tablets: Bottles of 3*, 14*, 20*, 42* or 100 tablets, Blister packs of 14* or 28* tablets.
KLACID Powder for Oral Liquid 250mg/5mL: Bottles containing 50mL, 70mL* and 100mL*.

* Strength/Pack size currently not marketed in Australia.

Store below 30ºC.

The reconstituted liquid can be used for up to 14 days when stored below 30ºC. The reconstituted liquid should not be refrigerated.

NAME AND ADDRESS OF THE SPONSOR

Abbott Australasia Pty Ltd
32-34 Lord Street
Botany, NSW 2019
POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

Date of TGA Approval: 20 June 1997

Date of most recent amendment: 12 April 2011

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