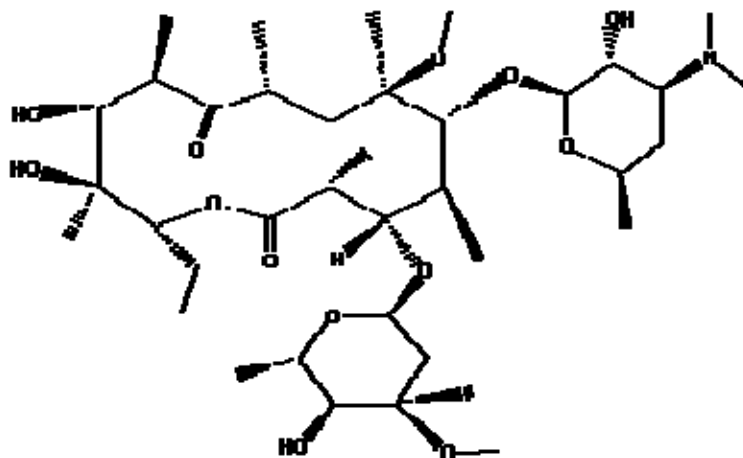


APO-CLARITHROMYCIN**NAME OF THE MEDICINE**

Clarithromycin.

Chemical Name: (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl- α -L-*ribo*-hexopyranosyl)oxy]-14-ethyl-12,13-dihydroxy-7-methoxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)- β -D-*xyl**o*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione;(6-*O*-methylerythromycin A).

Chemical Structure:



Molecular Structure: $C_{38}H_{69}NO_{13}$

Molecular Weight: 747.97

CAS Registry Number: 81103-11-9

DESCRIPTION

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.

PHARMACOLOGY

Clarithromycin is a semi-synthetic macrolide antibiotic.

Pharmacokinetics

Clarithromycin is absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg tablets is approximately 50%.

Food intake half an hour before tablet dosing increased both the rate and extent of clarithromycin absorption. In a study on the 250 mg tablets, the mean C_{max} and area under the plasma concentration curve (AUC) values were $0.72 \pm 0.27 \mu\text{g/mL}$ and $4.3 \pm 1.5 \mu\text{g.h/mL}$ (fasting) and $0.84 \pm 0.38 \mu\text{g/mL}$ and $4.7 \pm 1.7 \mu\text{g.h/mL}$ (non-fasting), respectively. The consequences for clinical efficacy of the increase in bioavailability caused by food are not known.

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 2-3 µg/mL with a 500 mg dose administered every 12 hours. The elimination half-life of clarithromycin was about 3 to 4 hours with 250 mg administered every 12 hours but increased to 5 to 7 hours with 500 mg administered every 12 hours. The non-linearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 12 hours but is quite marked at higher doses. With a 250 mg every 12 hours dosing, the principal metabolite, 14-hydroxy-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 dose of 500 mg every 12 hours, the peak steady-state concentrations of 14-hydroxy-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-hydroxy-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 central nervous system (CNS) is poor.

Concentration after 250 mg every 12 hours

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

Information was obtained regarding the penetration of clarithromycin in middle ear fluid in paediatric patients with otitis media. Approximately 2.5 hours after receiving the fifth dose (7.5 mg/kg twice daily) the mean concentration of clarithromycin was 2.53 µg/g fluid in the middle ear, and for the 14-hydroxy metabolite was 1.27 µg/g. The concentrations of parent drug and 14-hydroxy metabolite were variable, with two-thirds of patients having levels greater than the 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-hydroxy-clarithromycin which accounts for an additional 10-15% 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-hydroxy-clarithromycin concentrations were lower in hepatically impaired patients. The decreased formation of 14-hydroxy-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, C_{\max} , C_{\min} for both clarithromycin and its 14-hydroxy 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-hydroxy-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.

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 :

Usually Sensitive Bacteria	Non-Sensitive Bacteria
<i>Chlamydia pneumoniae</i> (TWAR)	Enterobacteriaceae
<i>Haemophilus influenzae</i>	<i>Pseudomonas</i> species
<i>Haemophilus parainfluenzae</i>	
<i>Helicobacter pylori</i>	
<i>Legionella pneumophila</i>	
<i>Moraxella (Branhamella) catarrhalis</i>	
<i>Mycobacterium avium</i>	
<i>Mycobacterium chelonae</i>	
<i>Mycobacterium intracellulare</i>	
<i>Mycoplasma pneumoniae</i>	
<i>Staphylococcus aureus</i>	
<i>Streptococcus pneumoniae</i>	
<i>Streptococcus pyogenes</i>	
α -haemolytic Streptococci (viridans group)	

Note :

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

The principal metabolite of clarithromycin in man is a microbiologically active metabolite, 14-hydroxy-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 *Strep. pneumoniae*, *Staph. aureus*, *Strep. 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" indicates 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 result 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.

Pharmacodynamics

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 the proposed doses. The clinical significance of these observations is not known. There are no data from long term animal carcinogenicity studies.

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.

CLINICAL TRIALS

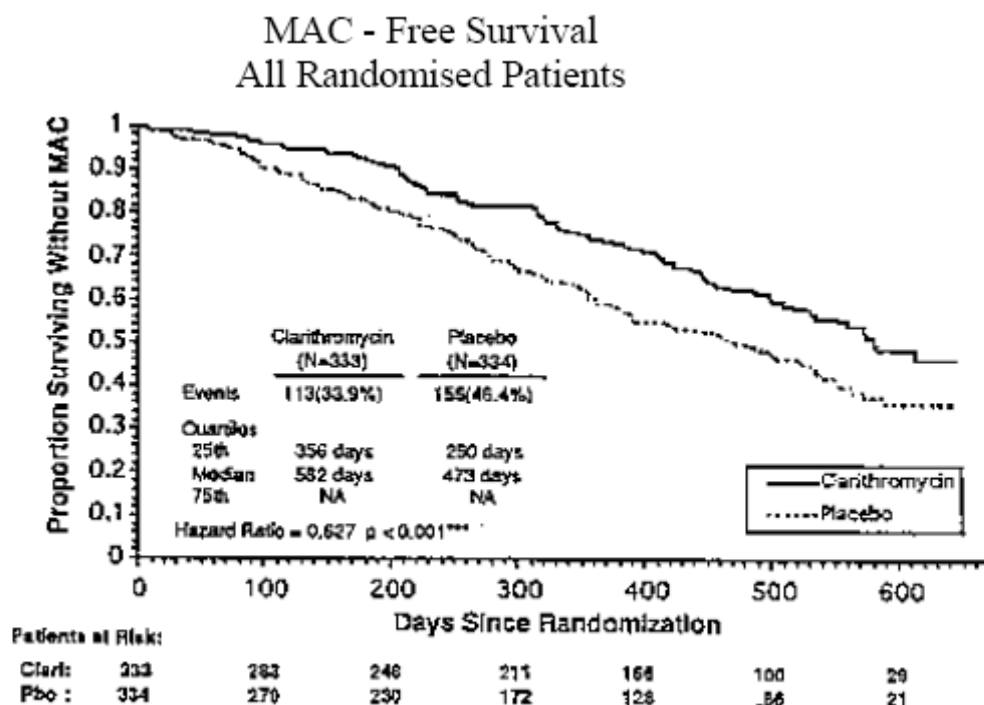
In a well controlled, double blind study, *H. pylori* infected duodenal ulcer patients received triple therapy with clarithromycin 500 mg bid (twice daily), amoxycillin 1000 mg bid and omeprazole 20 mg daily for 10 days or dual therapy with clarithromycin 500 mg tid (three times daily) and omeprazole 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 omeprazole 40 mg 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 56-68% (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/mm³, 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 figure below summarises the analysis of MAC free survival.



INDICATIONS

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 :

- Acute streptococcal pharyngitis;
- Community acquired pneumonia due to *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Streptococcus pneumoniae*;
- Uncomplicated skin and skin structure infections due to *Staphylococcus aureus* or *Streptococcus pyogenes*;
- 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.
- Prevention of disseminated *Mycobacterium avium* complex infection in HIV-infected adults with CD₄ lymphocyte counts < 75 cells/mm³ (see **PRECAUTIONS**). Disseminated infection due to *Mycobacterium avium* complex should be excluded by a negative blood culture prior to commencement of prophylaxis;
- Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*;
- Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

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 :

- Acute streptococcal pharyngitis and tonsillitis caused by *Streptococcus pyogenes*;
- Community acquired pneumonia including infections due to *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila*;

- Skin and skin structure infections (e.g. impetigo);
- Disseminated or localised infections due to *Mycobacterium avium* or *Mycobacterium intracellulare* in immunocompromised children, including those with HIV Infection or AIDS.
- 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 clarithromycin 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.

Clarithromycin is contraindicated as concurrent therapy with cisapride, pimozide, terfenadine, ergotamine or dihydroergotamine (see **PRECAUTIONS, Interactions with Other Medicines**).

PRECAUTIONS

General

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

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

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 *Cl. 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 (e.g. Lomotil), may prolong and/or worsen the condition and should not be used.

Risk-benefit should be considered when the following medical problems exist:

- In patients with severe renal failure (creatinine clearance 30 mL/min);
- In patients with hypokalaemia;
- History of ischaemic heart disease, ventricular arrhythmia, severe cardiac insufficiency, uncontrolled hypomagnesaemia, bradycardia (pulse < 50/min); or
- Concomitantly receiving other drugs known to prolong the QT interval (see **CONTRAINDICATIONS** and **Interactions with Other Medicines**).

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/mm³. Some authorities recommend delay of initiation of prophylaxis until the cell count has fallen to 50 cells/mm³.

Patients with Duodenal Ulcers

Patients with bleeding duodenal ulcers should be maintained on antisecretory 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 **PRECAUTIONS**, **Interactions with Other Medicines**, and **ADVERSE EFFECTS**).

Impaired Renal Function

Clarithromycin is principally excreted via the liver and kidney. Clarithromycin is contraindicated in patients with severe renal failure (creatinine clearance 30 mL/min). There is a progressive increase in peak concentrations and AUC of both clarithromycin and 14-OH-clarithromycin with decreasing renal function, together with a significant correlation between creatinine clearance and C_{max}, C_{min}, AUC and t_{1/2} for both parent and its 14- OH metabolite.

Clarithromycin must not be given with cisapride, pimozide or terfenadine because of the risk of lengthening of the QTc interval, leading to cardiac arrhythmias. For the same reason, clarithromycin is contraindicated in patients with hypokalaemia (see **CONTRAINDICATIONS**).

Impaired Hepatic Function

The AUC for 14-OH clarithromycin is markedly reduced in hepatic impaired patients and renal clearance of the parent drug, but not metabolite, is significantly increased. No dosage adjustment for clarithromycin appears necessary in patients with moderate or severe hepatic impairment, provided that renal function is unimpaired. Occasional elevation of hepatic transaminases (<1% incidence) and in frequent reports of severe but reversible hepatic dysfunction, including hepatocellular and/or cholestatic hepatitis, with or without jaundice with clarithromycin.

There is a case report of fatal progressive cholestatic liver disease in a woman with diabetes and chronic renal insufficiency following 3 days treatment with 500 mg clarithromycin.

See **Impaired Renal Function**

Use in the Elderly

Dosage adjustments are recommended in those patients with possible severe renal impairment (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**, **Impaired Renal Function**).

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.

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 appraised 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 (three with oral doses and one with intravenous dose 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 exposure in mice resulted in plasma levels 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 times higher than AUC values in humans given clarithromycin 500 mg twice daily.

The safety of clarithromycin for use in pregnancy has not been established.

Australian Categorisation Definition of Category B3 : Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

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.

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 torsades 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. Hence, concomitant use of these medications is contraindicated. (see **CONTRAINDICATIONS)**

Terfenadine. Clarithromycin affected terfenadine pharmacokinetics in a small study. Clarithromycin must not be given in association with terfenadine for patients with history of ischaemic heart diseases because of the risk of prolongation of QTc interval.

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. *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.

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 C_{min} and AUC of 33% and 18%, respectively. Steady-state concentrations of 14-hydroxy-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 creatinine clearance of 30-60 mL/min, the dose of clarithromycin should be reduced by 50%.
- For patients with creatinine clearance of < 30 mL/min, the dose of clarithromycin should be decreased by 75%.

Doses of clarithromycin greater than 1 mg/day should not be co-administered with ritonavir.

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 postmarketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs. Serum levels of these medications should be monitored during clarithromycin therapy.

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

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, tacrolimus, cyclosporin, rifabutin and sildenafil) may be associated with elevations in serum levels of these other drugs.

Hydroxymethylglutaryl coenzyme A reductase inhibitors. As with other macrolides, clarithromycin has been reported to increase concentrations of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (e.g. simvastatin, lovastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Omeprazole. Clarithromycin (500 mg every eight 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 to 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 coadministered with clarithromycin.

Oral anticoagulants. Spontaneous reports in the postmarketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. Prothrombin time should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously.

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. Coadministration 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 coadministered 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 clarithromycin 250 mg or 500 mg every 12 hours), the steady-state levels of C_{max}, C_{min} and 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 (such as Triazolam & Alprazolam) & Related Benzodiazepines (such as Midazolam)

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

Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is coadministered 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 post-marketing reports of drug interactions and CNS effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

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

Other Drug Interactions

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 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 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 postmarketing 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.

Administration of clarithromycin to patients receiving long-term digoxin may induce digoxin toxicity by increasing its bioavailability and blood concentrations by inhibiting *Eubacterium lentum*, a normal inhabitant of human gut flora and responsible for metabolism of digoxin.

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 2 hours. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspensions with zidovudine or didanosine.

Bidirectional drug interactions. Atazanavir. Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bidirectional 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 (ClCr 30 to 60 mL/minute), the dose of clarithromycin should be decreased by 50%. For patients with ClCr < 30 mL/minute, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1,000 mg/day should not be coadministered with protease inhibitors.

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

Saquinavir. Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bidirectional drug interaction. When saquinavir is coadministered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see above).

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_{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 (86%). At this time there are no data regarding concomitant administration of ketoconazole and clarithromycin.

Anticoagulants (Acenocoumarol, Warfarin) There have been reports of prolongation of prothrombin times in patients stabilised on the anticoagulant acenocoumarol when clarithromycin in doses of 250 mg b.d. to 500 mg b.d. were introduced, with an appropriate doubling of INR values. A similar interaction may exist with warfarin and it would be prudent to monitor the INR or prothrombin time in any patient on anticoagulant therapy and clarithromycin.

Cyclosporin Clarithromycin causes an approximate two-fold increase in AUC for cyclosporin, with halving of the clearance and in five transplant patients treated with cyclosporin A, the dose had to be reduced by one third when receiving clarithromycin concurrently.

Cabergoline Clarithromycin increases the plasma levels of cabergoline when co-administered in both healthy subjects and patients with Parkinson disease.

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%).

Adverse Effects Observed in Clinical Trials

BODY SYSTEM / FREQUENCY	<u>ADVERSE EVENT</u>	
	Clarithromycin 250 mg Tablets (n = 4,532)	Clarithromycin 500 mg Tablets (n = 658)
Body as a Whole		
Common	Infection, asthenia.	Fever.
Uncommon	Body aches and pains.	
Cardiovascular System		
Uncommon	Chest pain.	
Central Nervous System		
Common	Headache*, dizziness.	Headache.
Uncommon	Depression, sleep disturbance, tremor, flushing.	
Eye Disorders		
Uncommon	Photophobia.	

Digestive System		
Common	Nausea*, vomiting*, abdominal pain*, diarrhoea*, constipation*.	Nausea*, vomiting*, abdominal pain*, diarrhoea*.
Uncommon	Bleeding gums, heartburn, stomatitis, blood-stained stools.	Flatulence*, dyspepsia.
Haematopoietic and Lymphatic System		
Uncommon	Increased prothrombin time.	
Metabolic & Nutritional		
Common	Increases in ALT, AST*.	Increases in ALT, AST*, alkaline phosphatase.
Uncommon	Increases in LDH, alkaline phosphatase, bilirubin, urea nitrogen*.	
Musculoskeletal		
Uncommon	Back pain.	
Respiratory System		
Common		Dyspnoea*.
Skin and Skin Structure		
Common	Pruritus.	Rash*.
Uncommon	Pustular rash (non-urticarial), stained finger nails.	
Special Senses		
Uncommon	Taste perversion.	Taste perversion*.

* see **ADVERSE EFFECTS – Immunocompromised & 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 & 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 events by patients treated with total daily doses of 1000 mg to 2000 mg of clarithromycin were reported in the table above. The incidence is generally about 3 to 4 times more frequent for those patients treated with total daily doses of 4000 mg of clarithromycin.

Approximately 2-3% 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 ($< 2 \times 10^9/L$) or platelet ($< 75 \times 10^9/L$) 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 out of 13 patients on doses of clarithromycin between 1000 -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.

Adverse Effects Reported Spontaneously since Clarithromycin Tablets were Marketed

BODY SYSTEM	ADVERSE EFFECTS
Body as a Whole	Anaphylaxis, abdominal pain, asthenia allergic reaction, fever, headache.
Skin & Skin Structure	Stevens-Johnson Syndrome, urticaria, rash, pruritus, toxic epidermal necrolysis.
Central Nervous System	Anxiety, insomnia*, hallucinations, confusion, psychosis, vertigo, dizziness, dream abnormality, tinnitus, disorientation, depersonalization, nervousness, hyperkinesia, depression.
Haematopoietic & Lymphatic System	There have been rare reports of convulsions. Decreased white blood cell counts, decreased platelet counts, thrombocytopenia, leucopenia.
Metabolic & Nutritional	Increased serum creatinine, increased gamma-glutamyl transferase (GGT), hypoglycaemia.
Special Senses	Hearing disturbances, taste perversion, smell perversion, ageusia, anosmia, otitis media.
Digestive System	Dry mouth, tongue discolouration, glossitis, oral moniliasis, stomatitis, diarrhoea, nausea, vomiting, liver abnormalities, tooth discolouration, dyspepsia, enteritis.
Respiratory System	There have been rare reports of pancreatitis. Dyspnoea.
Urogenital System	Isolated cases of increased serum creatinine have been reported but an association has not been established. There have been reports of interstitial nephritis coincident with clarithromycin use.
Cardiac system.	Dysuria Torsades de pointes, electrocardiogram, QT prolonged, ventricular tachycardia.
Hepatobiliary system.	Hepatic failure, hepatitis, cholestatic hepatitis, cholestatic jaundice, hepatocellular jaundice, abnormal hepatic function.

There have been postmarketing 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, Colchicine** and **PRECAUTIONS**).

*see **ADVERSE EFFECTS – Immunocompromised & HIV / AIDS Patients**.

DOSAGE AND ADMINISTRATION

Patients with Non-Mycobacterial Infections

The usual recommended dosage of clarithromycin 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 (as 2 x 250 mg tablets) twice daily for 4 weeks is appropriate.

In patients with renal impairment with creatinine clearance < 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.

Patients with Peptic Ulcers

For the eradication of *H. pylori*, the recommended dosage regimen is clarithromycin 500 mg twice daily in conjunction with amoxycillin 1000 mg twice daily 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

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.

Experience in patients older than 65 years is limited. The recommended starting dose for elderly patients with calculated creatinine clearance > 30 mL/min is 500 mg twice daily. A further reduction of the initial dose and dose titration is recommended in those patients with possible severe renal impairment (see **PRECAUTIONS** and **ADVERSE EFFECTS**).

Clarithromycin should be used in conjunction with other anti-mycobacterial 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.

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 *M. avium* complex should be excluded by a negative blood culture prior to commencement of prophylaxis, and concurrent medication reviewed to avoid the possibility of drug interaction. Should prophylaxis fail, at least two other non-macrolide agents with good antimycobacterial activity should be chosen empirically, as the isolate of *M. 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*.

OVERDOSAGE

Symptoms

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.

Treatment

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.

Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdose.

PRESENTATION AND STORAGE CONDITIONS

APO-Clarithromycin 250 mg Tablets

Pale yellow, oval, film-coated tablets engraved “CLA250” on one side, “APO” on the other side.

Available in blister packs of 2*, 14, 28* and 100's*.

AUST R Number: 134850

Also available in bottles* of 14, 28 and 100's.

AUST R Number: 134865

APO-Clarithromycin 500 mg Tablets

Pale yellow, capsule-shaped, film-coated tablets engraved “CLA500” on one side, “APO” on the other side.

Available in blister packs of 3, 14, 20, 28, 42 and 100's.

AUST R Number: 134856

Also available in bottles of 14, 20, 28, 42 and 100's.

AUST R Number: 134883

(* : not marketed)

APO-Clarithromycin Tablets are intended for oral administration. Each tablet contains 250mg or 500 mg clarithromycin.

In addition, each tablet contains the following inactive ingredients :

microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal anhydrous silica, hypromellose, iron oxide yellow E172, titanium dioxide E171 and macrogol 8000.

Store below 30°C. Store in original package.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine.

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