



## APO-CLARITHROMYCIN

Clarithromycin 250 mg and 500 mg tablets

---

### Presentation

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

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

Apo-Clarithromycin tablets contain 250 mg or 500 mg of the active ingredient, clarithromycin.

Other ingredients in Apo-Clarithromycin 250 mg and 500 mg tablets are microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal anhydrous silica, hypromellose, iron oxide yellow (E172), titanium dioxide (E171) and macrogol 8000.

### Uses

#### **Actions**

#### **Microbiology**

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

Clarithromycin has demonstrated excellent *in vitro* activity against both standard strains of bacteria and clinical isolates. It is highly potent against a wide variety of aerobic and anaerobic Gram-positive and Gram-negative organisms. The minimum inhibitory concentrations (MIC) of clarithromycin are generally one log<sub>2</sub> dilution more potent than the MICs of erythromycin. *In vitro* data also indicate clarithromycin has excellent activity against *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Helicobacter (Campylobacter) pylori*. The *in vitro* and *in vivo* data show that this antibiotic has significant activity against clinically significant mycobacterial species.

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

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

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

#### **Aerobic Gram-Positive Microorganisms**

*Listeria monocytogenes*  
*Staphylococcus aureus*  
*Streptococcus pneumoniae*  
*Streptococcus pyogenes*

#### **Aerobic Gram-Negative Microorganisms**

## APO-CLARITHROMYCIN

Clarithromycin 250 mg and 500 mg tablets

---

*Haemophilus influenza*  
*Haemophilus parainfluenzae*  
*Legionella pneumophila*  
*Moraxella catarrhalis*  
*Neisseria gonorrhoeae*

### **Other Microorganisms**

*Chlamydia pneumoniae* (TWAR)  
*Mycoplasma pneumoniae*

### **Mycobacteria**

*Mycobacterium avium* complex (MAC) consisting of:  
*Mycobacterium avium*  
*Mycobacterium intracellulare*  
*Mycobacterium chelonae*  
*Mycobacterium fortuitum*  
*Mycobacterium kansasii*  
*Mycobacterium leprae*

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

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

### **Helicobacter**

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

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

### **Aerobic Gram-Positive Microorganisms**

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

### **Aerobic Gram-Negative Microorganisms**

*Bordetella pertussis*  
*Pasteurella multocida*

### **Anaerobic Gram-Positive Microorganisms**

*Clostridium perfringens*  
*Peptococcus niger*  
*Propionibacterium acnes*

## APO-CLARITHROMYCIN

### Clarithromycin 250 mg and 500 mg tablets

#### **Anaerobic Gram-Negative Microorganisms**

*Bacteroides melaninogenicus*

#### **Spirochetes**

*Borrelia burgdorferi*

*Treponema pallidum*

#### **Campylobacter**

*Campylobacter jejuni*

**Susceptibility Tests:** Quantitative methods that require measurement of zone diameters give the most precise estimates of susceptibility of bacteria to antimicrobial agents. One recommended procedure uses discs impregnated with 15 µg of clarithromycin for testing susceptibility (Kirby-Bauer diffusion test); interpretations correlate inhibition zone diameters of this disc test with MIC values for clarithromycin. The MICs are determined by the broth or agar dilution method. The recommended test medium for susceptibility testing of *H. influenzae* according to the National Committee of Clinical Laboratory Standards is the Haemophilus Test Medium (HTM).

The correlation of disc inhibition zone diameters with MICs is given in Table 1:

**Table 1: Clarithromycin Interpretive Standards**

ORGANISM	Inhibition Zone Diameter (mm)			MIC (µg/mL)		
	S	I	R	S	I	R
All organisms, except Haemophilus and Staphylococci	≥ 18	14–17	≤ 13	≤ 1	2–4	≥ 8
Staphylococci	≥ 20	-	≤ 19	≤ 0.5	-	≥ 1
<i>H. influenzae</i> , when tested on HTM*	≥ 13	11–12	≤ 10	≤ 8	16	≥ 32

S = susceptible I = intermediate R = resistant

HTM\* = Haemophilus Test Medium

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

## **APO-CLARITHROMYCIN**

### **Clarithromycin 250 mg and 500 mg tablets**

---

#### ***Pharmacokinetics***

The pharmacokinetics of orally administered clarithromycin has been studied extensively. These studies have shown that clarithromycin is readily and rapidly absorbed with an absolute bioavailability of approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change following multiple dosing.

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

#### ***In vitro***

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

#### **In Humans**

The principal metabolite of clarithromycin in humans and other primates is a microbiologically-active metabolite, 14-hydroxyclearithromycin. This metabolite is as active or 1–2 fold less active than the parent compound for most organisms, except for *H. influenzae* against which it is twice as active. The parent compound and the 14-hydroxy metabolite exert either an additive or synergistic effect on *H. influenzae in vitro* and *in vivo*, depending on bacterial strains.

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

#### **Concentration (after 250 mg every 12h)**

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

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

## APO-CLARITHROMYCIN

### Clarithromycin 250 mg and 500 mg tablets

---

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

In adults given single oral doses of 250 mg or 1200 mg clarithromycin, urinary excretion accounted for 37.9% of the lower dose and 46.0% of the higher dose. Faecal elimination accounted for 40.2% and 29.1% (this included a subject with only one stool sample containing 14.1%) of these respective doses.

#### Hepatic Impairment

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

#### Renal Impairment

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

#### Elderly Subjects

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

## **APO-CLARITHROMYCIN**

### **Clarithromycin 250 mg and 500 mg tablets**

---

#### **Concomitant Omeprazole Administration**

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

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

#### **Mycobacterium Avium Infections**

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

#### **Indications**

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

1. Respiratory tract infections including bronchitis, pneumonia, tonsillitis, sinusitis and pharyngitis.
2. Skin and soft tissue infections such as folliculitis, cellulitis and erysipelas.
3. Disseminated or localized mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare*. Localized infections due to *Mycobacterium chelonae*, *Mycobacterium fortuitum* or *Mycobacterium kansasii*.

## APO-CLARITHROMYCIN

### Clarithromycin 250 mg and 500 mg tablets

---

4. Prevention of disseminated *Mycobacterium avium* complex infection in HIV-infected patients with CD4 lymphocyte counts less than or equal to 100/mm<sup>3</sup>.

Clarithromycin in the presence of acid suppression is indicated for the treatment of duodenal ulcer and in reducing the rate of ulcer recurrence.

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

#### Triple Therapy

In a well-controlled double-blind study, *H. pylori* infected duodenal ulcer patients received triple therapy with clarithromycin 500 mg bd, amoxicillin 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 90% of the patients receiving clarithromycin triple therapy and in 60% of the patients receiving dual therapy.

#### Dual Therapy

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

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

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

## Dosage and Administration

### Adults

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

For dosage and administration in relation to food, refer to the '*Pharmacokinetics*' section.

### Renal Impairment

In patients 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.

### Dosage in Patients with Mycobacterial Infections

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

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

Treatment of other non-tuberculous mycobacterial infections should continue at the discretion of the physician.

### Dosage for MAC Prophylaxis

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

### Duodenal Ulcer

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

#### **Triple therapy regimen:**

- Clarithromycin 500 mg bd in conjunction with amoxicillin 1000 mg bd and omeprazole 20 mg daily for 7–10 days.
- Clarithromycin 500 mg, omeprazole 20 mg and amoxicillin 1000 mg all twice daily for one week.
- Clarithromycin 500 mg, amoxicillin 1000 mg, pantoprazole 40 mg all twice daily for one week.

#### **Dual therapy regimen:**

## APO-CLARITHROMYCIN

### Clarithromycin 250 mg and 500 mg tablets

---

- Clarithromycin 500 mg tid in conjunction with omeprazole 40 mg daily for 14 days, followed by omeprazole 20 mg or 40 mg daily for an additional 14 days (see **Further Information**).

### **Children**

For children older than 12 years, refer to the adult dosing.

Clarithromycin tablets are not recommended for children younger than 12 years.

## Contraindications

Clarithromycin is contraindicated in patients with a known hypersensitivity to macrolide antibiotics.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, pimozide and terfenadine and ergotamine or dihydroergotamine (see **Interactions**).

## Warnings and Precautions

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

### ***Pseudomembranous Colitis***

Pseudomembranous colitis has been reported with nearly all anti-bacterial agents, including macrolides, and may range in severity from mild to life-threatening. *Clostridium difficile*-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

### ***Myasthenia Gravis***

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

### ***Colchicine***

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

### ***Hepatic and Liver Impairment***

Clarithromycin is principally excreted by the liver and kidney. Therefore, caution should be exercised in administering this antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal failure.

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

### ***Pregnancy and Lactation***

**Category B3.** There are no adequate and well-controlled studies in pregnant women. Clarithromycin should not be used during pregnancy unless the potential benefit justifies a potential risk to the foetus.

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

### ***Mutagenesis and Impairment of Fertility***

Studies to evaluate the mutagenic potential of clarithromycin were performed using both non-activated and rat liver microsome-activated test systems (Ames test). Results of these studies provided no evidence of mutagenic potential at drug concentrations of 25 µg/petri plate or less. At a concentration of 50 µg/petri plate, the drug was toxic for all strains tested. A dominant lethal test in mice given at approximately 70 times the maximal human daily clinical dose was clearly negative for any mutagenic activity.

Fertility and reproduction studies have shown daily dosages of 150–160 mg/kg/day (10 times the maximal human dose) to male and female rats caused no adverse effects on the oestrous cycle, fertility, parturition or number and viability of offspring.

### ***Effects on the Ability to Drive and Use Machines***

Clarithromycin is not likely to affect the ability to drive or use machines.

## APO-CLARITHROMYCIN

Clarithromycin 250 mg and 500 mg tablets

### Adverse Effects

Table 2 lists adverse events reported in patients administered clarithromycin i.v. during clinical studies, as well as events seen with the oral formulation. Adverse events are listed by body system and frequency (common:  $\geq 1\%$ ).

#### Post-Marketing Experience

Table 3 lists adverse events for clarithromycin from post-marketing reports. As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to medicine exposure.

**Table 2: Adverse Events Reported in Clinical Trials**

System Organ Class	Frequency	Adverse Event
Nervous system disorders	Common	Headache Taste perversion
Gastrointestinal disorders	Common	Abdominal pain Diarrhoea Dyspepsia Nausea Vomiting
Investigations	Common	Hepatic enzyme increased

**Table 3: Adverse Events from Post-Marketing Surveillance Reports**

System Organ Class	Adverse Event
Infections and infestations	oral candidiasis
Blood and lymphatic system disorders	leukopenia thrombocytopenia
Immune System disorders	anaphylactic reaction hypersensitivity
Metabolism and nutrition disorders <sup>1</sup>	hypoglycaemia

## APO-CLARITHROMYCIN

### Clarithromycin 250 mg and 500 mg tablets

Psychiatric disorders	psychotic disorder hallucination disorientation confusional state depersonalization depression anxiety insomnia abnormal dreams
Nervous system disorders	convulsion dizziness ageusia anosmia dysgeusia parosmia
Ear and labyrinth disorders	deafness vertigo tinnitus
Cardiac disorders <sup>2</sup>	<i>torsade de pointes</i> electrocardiogram QT prolonged ventricular tachycardia
Gastrointestinal disorders	pancreatitis acute glossitis stomatitis tongue discoloration tooth discoloration
Hepatobiliary disorders <sup>3</sup>	hepatic failure hepatitis hepatitis cholestatic jaundice cholestatic jaundice hepatocellular hepatic function abnormal
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome toxic epidermal necrolysis urticaria rash
Renal and urinary disorders	nephritis interstitial
Investigations	blood creatinine increase hepatic enzyme increased

<sup>1</sup> There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin.

<sup>2</sup> As with other macrolides, QT prolongation, ventricular tachycardia, and *torsades de pointes* have rarely been reported with clarithromycin.

<sup>3</sup> 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.

## APO-CLARITHROMYCIN

### Clarithromycin 250 mg and 500 mg tablets

---

#### 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: Colchicine** and **Warnings and Precautions**).

#### Adverse Events in Immunocompromised Patients

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

In adult patients, the most frequently reported adverse effects by patients treated with total daily doses of 1000 mg and 2000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance and SGOT & SGPT elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth.

In immunocompromised patients, evaluations of laboratory values were made by analyzing those values outside the seriously abnormal level (*i.e.* the extreme high or low limit) for the specified test. On the basis of this criteria, about 2% to 3% of these patients who received 1000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated BUN levels.

## Interactions

The use of the following medicines is strictly contraindicated due to the potential for severe medicine 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**).

#### 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 *torsade de pointes*. In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a 2–3 fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval, which did not lead to any clinically

## **APO-CLARITHROMYCIN**

### **Clarithromycin 250 mg and 500 mg tablets**

---

detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

#### **Ergotamine/Dihydroergotamine**

Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues, including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated (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-hydroxyclearithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-hydroxyclearithromycin 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 minimum clarithromycin concentration ( $C_{min}$ ) and area under the curve (AUC) of 33% and 18%, respectively. Steady-state concentrations of the active metabolite 14-hydroxyclearithromycin 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]-hydroxyclearithromycin 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:

- patients with creatinine clearance 30 to 60 mL/min, the dose of clarithromycin should be reduced by 50%; and
- patients with creatinine clearance < 30 mL/min, the dose of clarithromycin should be decreased by 75%.

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

## **APO-CLARITHROMYCIN**

Clarithromycin 250 mg and 500 mg tablets

---

### ***Effects of Clarithromycin on Other Medicinal Products***

#### **Antiarrhythmics**

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

#### **CYP3A-Based Interactions**

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

Clarithromycin should be used with caution in patients receiving treatment with other medicines known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolized by this enzyme. Dosage adjustments may be considered and when possible, serum concentrations of medicines primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

The following medicines or medicine classes are known or suspected to be metabolized by the same CYP3A isozyme:

alprazolam	astemizole	carbamazepine	cilostazol
cisapride	cyclosporine	disopyramide	ergot alkaloids
lovastatin	methylprednisolone	midazolam	omeprazole
oral anticoagulants (e.g. warfarin)		pimozide	quinidine
rifabutin	sildenafil	simvastatin	tacrolimus
terfenadine	triazolam	vinblastine.	

Medicines interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

#### **HMG-CoA Reductase Inhibitors**

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

#### **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 ( $C_{max}$ ,  $AUC_{0-24}$  and  $t_{1/2}$  increased by 30%, 89% and 34%, respectively) by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with clarithromycin.

## **APO-CLARITHROMYCIN**

### **Clarithromycin 250 mg and 500 mg tablets**

---

#### **Oral Anticoagulants**

Spontaneous post-marketing reports 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; CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these medicines are co-administered with clarithromycin.

#### **Theophylline and Carbamazepine**

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

#### **Tolterodine**

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

#### **Triazolobenzodiazepines (e.g. Triazolam and Alprazolam) and Related Benzodiazepines (e.g. Midazolam)**

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after i.v. administration of midazolam and 7-fold after oral administration. 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 metabolized by CYP3A, including triazolam and alprazolam. There have been post-marketing reports of medicine interactions and central nervous system (CNS) effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

For benzodiazepines, which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

### ***Other Medicine 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 **Warnings and 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 post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentration should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

#### **Zidovudine**

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

### ***Bi-directional Medicine Interactions***

#### **Atazanavir**

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A and there is evidence of a bi-directional medicine interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-hydroxyclearithromycin, with a 28% increase in the AUC of atazanavir.

Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with renal impairment, the following dosage adjustments should be considered:

- patients with creatinine clearance 30 to 60 mL/min, the dose of clarithromycin should be reduced by 50%; and
- patients with creatinine clearance < 30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation.

Doses of clarithromycin greater than 1 g/day should not be co-administered with protease inhibitors.

## **APO-CLARITHROMYCIN**

### **Clarithromycin 250 mg and 500 mg tablets**

---

#### **Itraconazole**

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

#### **Saquinavir**

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A and there is evidence of a bi-directional medicine interaction. Concomitant administration of clarithromycin (500 mg bd) and saquinavir (soft gelatin capsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state AUC and  $C_{max}$  values of saquinavir which were 177% and 187% higher, respectively, than those seen with saquinavir alone. Clarithromycin AUC and  $C_{max}$  values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two medicines are co-administered for a limited time at the doses/formulations studied. Observations from medicine interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from medicine interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see Interactions).

#### **Verapamil**

Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

#### ***Oral Contraceptives***

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

## **Overdosage**

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disease ingested 8 g of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia.

Adverse reactions accompanying overdose should be treated by the prompt elimination of 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, contact the New Zealand Poisons Information Centre on 0800 764 766.



## **APO-CLARITHROMYCIN**

Clarithromycin 250 mg and 500 mg tablets

---

### **Pharmaceutical Precautions**

Storage conditions: store below 30°C.  
Shelf life: 3 years.

### **Medicine Classification**

Prescription Medicine

### **Package Quantities**

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

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

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

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

### **Further Information**

Nil

### **Name and Address**

Apotex NZ Ltd  
32 Hillside Road  
Glenfield  
AUCKLAND

### **Date of Preparation**

8 July 2009