

# Data Sheet

## CLARAC

### *Clarithromycin Ph.Eur 250 mg Tablets*

---

## Presentation

---

Clarac 250 mg Tablets are bright yellow drapsule shaped tablets, engraved with 'CLA' on one side and '250' engraved on the other side.

Dimensions 8.00 mm in diameter and 15.60 mm in length.

---

## Uses

---

### **Actions**

### **Microbiology**

Clarithromycin is a macrolide antibiotic. Clarithromycin exerts its antibacterial action by binding to the 50 S 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 *Helicobacter pylori*, with activity greater at neutral pH than at acid pH.

Clarithromycin has been shown to be active against most strains of the following micro-organisms 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**

*Haemophilus influenzae*  
*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**

*Helicobacter pylori*

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

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

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

*Streptococcus agalactiae*

*Streptococci (Group C, F, G)*

*Viridans group streptococci*

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

*Bordetella pertussis*

*Pasteurella multocida*

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

*Clostridium perfringens*

*Peptococcus niger*

*Propionibacterium acnes*

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

*Bacteroides melaninogenicus*

### **Spirochetes**

*Borrelia burgdorferi*

*Treponema pallidum*

### **Campylobacter**

*Campylobacter jejuni*

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

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 MIC's are determined by the broth or agar dilution method. The recommended test medium for susceptibility testing of *Haemophilus influenzae* according to the National Committee of Clinical Laboratory Standards (NCCLS) is the Haemophilus Test Medium (HTM).

The correlation of disc inhibition zone diameters with MIC's is given in the following table:

### **Clarithromycin Interpretive Standards**

Organisms	Inhibition Zone Diameter (mm)			MIC $\mu$ g/ml)		
	S	I	R	S	I	R
<b>All Organisms (except Haemophilus and Staphylococci)</b>	$\geq 18$	14-17	$\leq 13$	$\leq 1$	2-4	$\geq 8$
<b>Staphylococci</b>	$\geq 20$	-	$\leq 19$	$\leq 0.5$	-	$\geq 1$
<b>Haemophilus influenzae when tested on HTM*</b>	$\geq 13$	11-12	$\leq 10$	$\leq 8$	16	$\geq 32$

\* HTM - Haemophilus Test Medium

S = susceptible I = intermediate R = resistant

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).

### **Pharmacokinetics**

The pharmacokinetic 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  $\mu$ g/ml. A decrease in binding to 41% at 45.0  $\mu$ g/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**

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.

<b>Concentration (after 250 mg q 12h)</b>		
<b>Tissue Type</b>	<b>Tissue (<math>\mu\text{g/g}</math>)</b>	<b>Serum (<math>\mu\text{g/ml}</math>)</b>
Tonsil	1.6	0.8
Lung	8.8	1.7

With BID dosing at 250 mg, the peak steady state plasma concentration was attained in 2 to 3 days and averaged about 1  $\mu\text{g/ml}$  for clarithromycin and 0.6  $\mu\text{g/ml}$  for 14-hydroxy- clarithromycin, while the elimination half-lives of the parent drug and metabolite were 3-4 hours and 5-6 hours, respectively. With BID dosing at 500 mg, the steady state  $C_{\text{max}}$  for clarithromycin and its hydroxylated metabolite were achieved by the fifth dose. After the fifth and seventh doses the  $C_{\text{max}}$  for clarithromycin averaged 2.7 and 2.9  $\mu\text{g/ml}$ ; and its hydroxylated metabolite averaged 0.88 and 0.83  $\mu\text{g/ml}$  respectively. The half-life of the parent drug at the 500 mg dose level was 4.5 to 4.8 hours, while that of 14-hydroxy-clarithromycin was 6.9-8.7 hours. At steady state the 14-hydroxy-clarithromycin levels did not increase proportionately with the clarithromycin dose, and the apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at the higher doses. This non-linear pharmacokinetic behaviour of clarithromycin, coupled with the overall decrease in the formation of 14-hydroxylation and N-demethylation products at the higher doses, indicates 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 liver impairment who were given 250 mg of clarithromycin BID 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 of 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 parent drug and 14-hydroxy metabolite. However, there was no difference between the 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.

### **Concomitant Omeprazole Administration**

A pharmacokinetic study was conducted with clarithromycin 500 mg TID and omeprazole 40 mg QD. When clarithromycin was given alone at 500 mg q8h, the mean steady state  $C_{max}$  value was approximately 3.8  $\mu\text{g/ml}$  and the mean  $C_{min}$  value was approximately 1.8  $\mu\text{g/ml}$ . The mean  $AUC_{0-8}$  for clarithromycin was 22.9  $\mu\text{g}\cdot\text{hr/ml}$ . 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-hydroxy-clarithromycin observed following administration of usual doses to adult patients with HIV infection were similar to those observed in normal subjects. However, at the higher doses which may be required to treat mycobacterial infections, clarithromycin concentrations were much higher than those observed at the usual doses. In adult HIV-infected patients taking 2000 mg/day in two divided doses, steady state clarithromycin  $C_{max}$  values ranged from 5-10  $\mu\text{g/ml}$ .  $C_{max}$  values as high as 27  $\mu\text{g/ml}$  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*.
4. Prevention of disseminated *Mycobacterium avium* complex infection in HIV-infected patients with CD4 lymphocyte counts less than or equal to  $100/\text{mm}^3$ .
5. Duodenal ulcer. 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 BID, amoxicillin 1000 mg BID 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 (as 2 x 250 mg tablets) 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, see under 'pharmacokinetics' section.

**Renal impairment:** In patients with creatinine clearance less than 30 ml/min, the dosage of clarithromycin should be reduced by one-half, ie., 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 (as 2 x 250 mg tablets) 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 (as 2 x 250 mg tablets) twice daily.

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

***Triple therapy regimen:*** Clarithromycin 500 mg (as 2 x 250 mg tablets) BID in conjunction with amoxicillin 1000 mg BID and omeprazole 20 mg daily for 7 - 10 days.

Clarithromycin 500 mg (as 2 x 250 mg tablets), omeprazole 20 mg and amoxicillin 1000 mg all twice daily for one week.

Clarithromycin 500 mg (as 2 x 250 mg tablets), amoxicillin 1000 mg, pantoprazole 40 mg all twice daily for one week.

***Dual therapy regimen:*** Clarithromycin 500 mg (as 2 x 250 mg tablets) 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

---

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.

Pseudomembranous colitis has been reported with nearly all anti-bacterial agents, including macrolides, and may range in severity from mild to life-threatening.

Presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

### ***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.

---

## Adverse Effects

---

Clarithromycin is generally well-tolerated. The most frequently reported side effects of clarithromycin in clinical studies were gastrointestinal related, ie. nausea, dyspepsia, abdominal pain, vomiting and diarrhoea. Other reported side effects include headache, taste perversion, and transient elevations of liver enzymes.

## ***Post-Marketing Experience***

As with other macrolides, hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. 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.

Isolated cases of increased serum creatinine have been reported but an association has not been established.

Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis and Stevens-Johnson Syndrome/toxic epidermal necrolysis have occurred with orally administered clarithromycin. There have been reports of transient central nervous system side effects ranging from dizziness, vertigo, anxiety, insomnia, bad dreams, tinnitus, confusion, disorientation, hallucination, psychosis and depersonalisation. However, a cause and effect relationship has not been established.

There have been reports of hearing loss with clarithromycin which is usually reversible upon withdrawal of therapy. Reports of alteration of the sense of smell, usually in conjunction with taste perversion have also been reported.

As with other macrolides QT prolongation, ventricular tachycardia, and torsades de pointes have rarely been reported with clarithromycin.

Glossitis, stomatitis, oral monilia and tongue discolouration have been reported with clarithromycin therapy.

There have been reports of tooth discolouration in patients treated with clarithromycin. Tooth discolouration is usually reversible with professional dental cleaning.

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

Isolated cases of leukopenia and thrombocytopenia have been reported.

There have been rare reports of pancreatitis and convulsions.

There have been reports of interstitial nephritis coincident with clarithromycin use.

Interaction with cisapride: prolongation of the QT interval and cardiac arrhythmias.

Adverse laboratory changes: Abnormal liver function test results may occur following therapy with clarithromycin. Changes in laboratory parameters without regard to drug relationship are as follows:

**Hepatic:** elevated SGPT (ALT), SGOT (AST), GGT, alkaline phosphatase, LDH, bilirubin

**Haematologic:** decreased WBC, platelet count, elevated prothrombin

**Renal:** elevated BUN, serum creatinine

### ***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, SGOT and SGPT elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth.

In these immunocompromised patients, evaluations of laboratory values were made by analyzing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of this 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.

The incidences were comparable with patients treated with 1000 mg and 2000 mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000 mg of clarithromycin. In these immunocompromised patients elevations of laboratory values were made by analyzing those values outside the seriously abnormal level (ie. 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 or 2000 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**

---

### ***Cytochrome P450 Interactions***

Data available to date indicate clarithromycin is metabolised primarily by hepatic cytochrome P450 3A (CYP3A) isozyme. This is an important mechanism determining many drug interactions. The metabolism of other drugs by this system may be inhibited by concomitant administration with

clarithromycin and may be associated with elevations in serum levels of these other drugs.

The following drugs or drug classes are known or suspected to be metabolised by the same CYP3A isozyme:

Alprazolam astemizole carbamazepine cilostazol

Cisapride cyclosporine disopyramide ergot alkaloids

Lovastatin methylprednisolone midazolam omeprazole

Pimozide quinidine rifabutin sildenafil

Simvastatin tacrolimus terfenadine triazolam

Vinblastine warfarin

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

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 drugs were administered concomitantly with clarithromycin.

The following CYP3A based drug interactions have been observed with erythromycin products and/or with clarithromycin in post-marketing experience:

Rhabdomyolysis coincident with the co-administration of clarithromycin and the HMG-CoA reductase inhibitors, lovastatin and simvastatin, has rarely been reported.

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

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

There have been reports of Torsades de Pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Serum levels of these medications should be monitored during clarithromycin therapy.

Post marketing reports indicate that coadministration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm and ischemia of the extremities and other tissues including the central nervous system.

### ***Other Drug Interactions***

Elevated digoxin serum concentrations have been reported in patients receiving clarithromycin tablets and digoxin concomitantly. Monitoring of serum digoxin levels should be considered.

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.

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

### ***Antiretroviral Drug Interactions***

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.

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

---

## **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.

---

## **Pharmaceutical Precautions**

---

Store below 30°C in a well-closed container and protect from light. Shelf life is 3 years.

---

## **Medicine Classification**

---

Prescription Medicine

---

## **Package Quantities**

---

Clarac 250 mg Tablets are available in packs of 2's, 10's, 14's and 100's.

---

## **Further Information**

---

Clarac 250 mg Tablets contain microcrystalline cellulose, maize starch, croscarmellose sodium, povidone, stearic acid, magnesium stearate, silicone dioxide, Opadry white, hypromellose, Eurolake quinoline yellow and vanillin.

---

## **Name and Address**

---

Douglas Pharmaceuticals Ltd  
P O Box 45-027  
AUCKLAND 0651  
Ph: (09) 835-0660  
Fax: (09) 835-0665

---

## **Date of Preparation**

---

13 March 2008

