CLARIZA
(Clarithromycin)

250mg & 500mg

Tablets

COMPOSITION

Each film coated tablet contains:
Clarithromycin ……250mg
(U.S.P. Specification)

Each film coated tablet contains:
Clarithromycin…….. 500mg
(U.S.P. Specification)

THERAPEUTIC INDICATIONS

Clarithromycin film-coated tablets are indicated for the treatment of the following bacterial infections, when caused by clarithromycin-susceptible bacteria
• Bacterial pharyngitis
• Mild to moderate community acquired pneumonia
• Acute bacterial sinusitis (adequately diagnosed)
• Acute exacerbation of chronic bronchitis
• Skin infections and soft tissue infections of mild to moderate severity,
• In appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing agent for the eradication of Helicobacter pylori in patients with Helicobacter pylori associated ulcers.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

DOSAGE AND METHOD OF ADMINISTRATION

The dosage of Clarithromycin film-coated tablets depends on the type and severity of the infection and has to be defined in any case by the physician.
Adults and adolescents (12 years and older)
• Standard dosage: The usual dose is 250 mg twice daily (in the morning and in the evening)
• High dosage treatment (severe infections): The usual dose may be increased to 500 mg twice daily in severe infections.
Children younger than 12 years:
Use of Clarithromycin film-coated tablets is not recommended for children younger than 12 years with a body weight less than 30 kg. Clinical trials have been conducted using clarithromycin pediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin pediatric suspension.
For children with a body weight of more than 30kg, the dose for adults apply.
Dosage in renal functional impairment:
In patients with renal impairment with creatinine clearance less than 30 mL/min, the dosage of clarithromycin should be reduced by one-half, i.e., 250 mg once daily, or 250 mg twice daily in more severe infections. Treatment should not be continued beyond 14 days in these patients.
Patients with hepatic impairment:
Caution should be exercised when administrating clarithromycin in patients with hepatic impairment.
H. pylori eradication in peptic ulcer disease
For the eradication of *H. pylori,* the selection of antibiotics should consider the individual patient's drug tolerance, and should be undertaken in accordance with national, regional and local resistance patterns and treatment guidelines.
Usually, clarithromycin is administered in combination with another antibiotic and a proton-pump inhibitor for one week.
The therapy may be repeated if the patient is still H. pylori-positive
Duration of therapy:
The duration of therapy with Clarithromycin film-coated tablets depends on the type and severity of the infection and has to be defined in any case by the physician.
• The usual duration of treatment is 7 to 14 days.
• Therapy should be continued at least for 2 days after symptoms have subsided.
• In Streptococcus pyogenes (group A beta-haemolytic streptococcus) infections the duration of therapy should be at least 10 days.
• Combination therapy for the eradication of H. pylori infection should be continued for 7 days.

Method of administration

The tablet should be swallowed whole with a sufficient amount of fluid (e.g., one glass of water).
Clarithromycin film-coated tablets may be given irrespective of food intake.

CONTRAINDICATIONS

Clarithromycin is contraindicated in patients with known hypersensitivity to the active substance clarithromycin, to other macrolides or to any of the excipients
Concomitant administration of clarithromycin and any of the following active substances is contraindicated: astemizole, cisapride, pimozide and terfenadine as this may result in QT prolongation (congenital or documented acquired QT prolongation) and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes.
Concomitant administration with ticagrelor or ranolazine is contraindicated.
Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated, as this may result in ergot toxicity.
Concomitant administration of clarithromycin and lomitapide is contraindicated.
Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointe.
Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.
Clarithromycin should not be given to patients with electrolyte disturbances (hypokalemia or hypomagnesaemia, due to the risk of prolongation of the QT interval).
Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
As with other strong CYP3A4 inhibitors, Clarithromycin should not be used in patients taking colchicine.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy

Caution is advised in patients with severe renal insufficiency.

Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.
Cases of fatal hepatic failure have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhea 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 diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.
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. Concomitant administration of clarithromycin and colchicines is contraindicated.

Caution is advised regarding concomitant administration of clarithromycin and triazolo benzodiazepines, such as triazolam, and midazolam.
Caution is advised regarding concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides. Monitoring of vestibular and auditory function should be carried out during and after treatment.

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in treatment with macrolides including clarithromycin. Therefore, as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes), clarithromycin should be used with caution in the following patients;

• Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia
• Clarithromycin must not be given to patients with hypokalemia

• Patients concomitantly taking other medicinal products associated with QT prolongation
• Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfendine is contraindicated
• Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia
Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.

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

Skin and soft tissue infections of mild to moderate severity, these infections are most often caused by Staphylococcus aureus and Streptococcus pyogenes, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed. In cases where beta–lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the drug of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections, such as those caused by Corynebacterium minutissimum, acne vulgaris, and erysipelas and in situations where penicillin treatment cannot be used.
In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g., Acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome, and toxic epidermal necrolysis, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.
Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

Cisapride, pimozide, astemizole and terfenadine
Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades 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 torsades de pointes. In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a two-to-three-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.

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.

HMG-CoA Reductase Inhibitors (statins)
Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.
Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g., Fluvastatin) can be considered. Patients should be monitored for signs and symptoms of myopathy.

Effects of other medicinal products on clarithromycin

Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St. Johns wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to a reduced efficacy. Furthermore it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inhibitor administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.
The following drugs are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dosage adjustment or consideration of alternative treatments may be required.

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

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

Fluconazole
Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir
A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted.

Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 g/day should not be coadministered with ritonavir.
Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see section below, Bi-directional drug interactions).

Effect of clarithromycin on other medicinal products

CYP3A-based interactions
Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolized by this enzyme.
Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.
The following drugs or drug 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, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine but this list is not comprehensive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Direct acting oral anticoagulants (DOACs)
The DOAC dabigatran is a substrate for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolized via CYP3A4 and are also substrates for P-gp. Caution should be exercised when clarithromycin is co-administered with these agents particularly to patients at high risk of bleeding

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 QT prolongation during co-administration of clarithromycin with these drugs. Serum levels of quinidine and disopyramide should be monitored during clarithromycin therapy.
There have been post marketing reports of hypoglycemia with the concomitant administration of clarithromycin and disopyramide. Therefore, blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

Oral hypoglycemic agents/Insulin
With certain hypoglycemic drugs such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycemia when used concomitantly. Careful monitoring of glucose is recommended.

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

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

Theophylline, 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 drugs were administered concomitantly with clarithromycin. Dose reduction may need to 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 metabolizer population.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam)
When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous 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.
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 central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Other drug interactions

Aminoglycosides
Caution is advised regarding concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides.

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

Digoxin
Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of 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 concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine
Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine to allow for a 4-hour interval between each medication. This interaction does not appear to occur in pediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and Valproate
There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolized by CYP3A (e.g., phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported
Concomitant administration of clarithromycin with lomitapide is contraindicated due the potential for markedly increased transaminases

Bi-directional drug interactions

Atazanavir
Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2- fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH-clarithromycin, with a 28% increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased

by 50%. For patients with creatinine clearance <30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation.
Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

Calcium Channel Blockers
Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

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 pharmacologic effect.

Saquinavir
Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in steady-state AUC and Cmax values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and Cmax values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are co-administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug 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

FERTILITY, PREGNANCY AND LACTATION

Pregnancy
The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embryofetal development cannot be excluded. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risks.
Breast-feeding
The safety of clarithromycin for use during breast feeding of infants has not been established. Clarithromycin is excreted into human breast milk in small amounts. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin.
Fertility
There is no data available on the effect of clarithromycin on fertility in humans. In rats, the limited data available do not indicate any effects on fertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

ADVERSE DRUG REACTIONS

a. Summary of the safety profile
The most frequent and common adverse reactions related to clarithromycin therapy for both adult and pediatric populations are abdominal pain, diarrhea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics.
There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without preexisting mycobacterial infections.
b. Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin immediate-release tablets, granules for oral suspension, powder for solution for injection, extended-release tablets and modified-release tablets.
The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

System Organ Class	Very common (≥1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥1/1,000 to < 1/100	Not Known (cannot be estimated from the available data)
Infections and infestations			Cellulitis[1], candidiasis, gastroenteritis[2], infection[3], vaginal infection	Pseudomembranous colitis, erysipelas
Blood and lymphatic system			Leukopenia, neutropenia[4], thrombocythemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders[5]			Anaphylactoid reaction[1], Hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety, nervousness[3],	Psychotic disorder, confusional state, depersonalization, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache, taste perversion	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[6], tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing, impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged[7], extrasystoles[1], palpitations	Torsade de pointes[7], ventricular tachycardia[7] ventricular fibrillation
Vascular disorders		Vasodilation[1]		Hemorrhage[8]
Respiratory, thoracic and mediastinal disorder			Asthma[1], epistaxis[2], pulmonary embolism[1]	
Gastrointestinal disorders		Diarrhea[9], vomiting, dyspepsia, nausea, abdominal pain	Esophagitis[1], gastroesophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence	Pancreatitis acute, tongue discoloration, tooth discoloration

Hepatobiliary disorders		Liver function test abnormal	Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased4	Hepatic failure[10], jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous[1], pruritus, urticaria, rash maculo-papular[3]	Stevens-Johnson syndrome[5], toxic epidermal necrolysis[5], drug rash with eosinophilia and systemic symptoms (DRESS), acne, acute generalized exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders			Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis[2, 11], myopathy
Renal and urinary disorders			Blood creatinine increased[1], blood urea increased[1]	Renal failure, nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis[1]	Injection site pain[1], injection site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]	
Investigations			Albumin globulin ratio abnormal[1] , blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4]	International normalized ratio increased[8], prothrombin time prolonged[8], urine color abnormal

[1] ADRs reported only for the Powder for Solution for Injection formulation
[2]ADRs reported only for the Extended-Release Tablets formulation
[3] ADRs reported only for the Granules for Oral Suspension formulation
[4] ADRs reported only for the Immediate-Release Tablets formulation
[5], [7, 9, 10,] See section a)
[6, 8, 11] See section c)

c. Description of selected adverse reactions
Injection site phlebitis, injection site pain, vessel puncture site pain, and injection site inflammation are specific to the clarithromycin intravenous formulation.
In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol
There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in elderly and/or patients with renal insufficiency, some with a fatal outcome
There have been post-marketing reports of drug 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
There have been rare reports of clarithromycin ER tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g. suspension) or another antibiotic.
Special population: Adverse Reactions in Immunocompromised Patients (see section e)

d. Paediatric populations
Clinical trials have been conducted using clarithromycin pediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin pediatric suspension. There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age.
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

e. Other special populations
Immunocompromised patients
In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of Human Immunodeficiency Virus (HIV) disease or intercurrent illness.
In adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 1,000 mg and 2,000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhea, rash, flatulence, headache, constipation, hearing disturbance, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvate Transaminase (SGPT) elevations. Additional low-frequency events included dyspnea, insomnia and dry mouth. The incidences were comparable for patients treated with 1,000 mg and 2,000 mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4,000 mg of clarithromycin.
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 these criteria, about 2% to 3% of those patients who received 1,000 mg or 2,000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormal values were noted for patients who received 4,000 mg daily for all parameters except White Blood Cell.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

OVERDOSE

Symptoms of intoxication:
Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested eight grams of clarithromycin and showed altered mental status, paranoid behavior, hypokalemia and hypoxemia.
Therapy of intoxication:
Adverse reactions accompanying overdosage 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 hemodialysis or peritoneal dialysis.
In the case of overdosage, clarithromycin IV (powder for solution for injection) should be discontinued and all other appropriate supportive measures should be instituted.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Macrolides
ATC code: J01FA09
Mode of action:
Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.
The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or twofold higher than the MICs of the parent compound, except for H. influenzae where the 14-hydroxy metabolite is two-fold more active than the parent compound.
PK/PD relationship
Clarithromycin is extensively distributed into body tissues and fluids. Due to the high tissue penetration, intracellular concentrations higher than serum concentrations. The main pharmacodynamic parameters to predict macrolide activities are unconvincing established. The time above the MIC (T / MIC) is the best determinant for the efficacy of clarithromycin. Because the concentrations of clarithromycin in the lung tissues and epithelial tissue fluid reaches the plasma concentrations exceed, the use of plasma

concentrations-based parameters are insufficient to accurately predict response for respiratory infections.

Mechanisms of resistance:

Resistance mechanisms against macrolide antibiotics include alteration of the target site of the antibiotic or are based on modification and/or the active efflux of the antibiotic. Resistance development can be mediated via chromosomes or plasmids, be induced or exist constitutively. Macrolide resistant bacteria generate enzymes which lead to methylation of residual adenine at ribosomal RNA and consequently to inhibition of the antibiotic binding to the ribosome. Macrolide-resistant organisms are generally cross-resistant to lincosamides and streptogramine B based on methylation of the ribosomal binding site. Clarithromycin ranks among the strong inducers of this enzyme as well. Furthermore, macrolides have a bacteriostatic action by inhibiting the peptidyl transferase of ribosomes. A complete cross-resistance exists among clarithromycin, erythromycin and azithromycin. Methicillin-resistant staphylococci and penicillin-resistant Streptococcus pneumoniae are resistant to macrolides such as clarithromycin.

Breakpoints:

The following breakpoints for clarithromycin, separating susceptible organisms from resistant organisms, have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST) 2010-04-27 (v 1.1)

		Species-related break points (S</R>)														Non species related break points S</R>
		Enterobacteriaceae	*Pseudomonas*	*Acinetobacter*	*Staphylococcus*	*Enterococcus*	*Streptococcus A,B,C,G*	*S.pneumoniae*	Other streptococci	*H.influenzae*	*M.catarrhalis*	*N.gonorrhoeae*	*N.meningitidis*	*Gram –negative anaerobes*	*Gram-positive anaerobes*	
Clarithromycin[B,C]																IE

[A] Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table or footnotes However, pharmacodynamic data for calculation of macrolide, lincosamines and streptogramins non-species related breakpoints are not robust, hence IE.

[B] Erythromycin can be used to determine the susceptibility of the listed bacteria to the other macrolides (azithromycin, clarithromycin and roxithromycin

[C] Clarithromycin is used for the eradication of H. pylori (MIC ≤0.25 mg/L for wild type isolates).

[D] The correlation between H. influenzae macrolide MICs and clinical outcome is weak. Therefore, breakpoints for macrolides and related antibiotics were set to categorize wild type H. influenzae as intermediate.

Clarithromycin is used for the eradication of H. pylori; minimum inhibitory concentration (MIC) ≤ 0.25 µg/ml which has been established as the susceptible breakpoint by the Clinical and Laboratory Standards Institute (CLSI).

Susceptibility:

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalance of resistance is such that the utility of the agent in atleast some types of infections is questionable.

Commonly susceptible species
Aerobic, Gram-positive microorganisms
Streptococcus group F
Corynebacterium diptheriae
Aerobic, Gram-negative microorganisms
Bordetella pertusis
Moraxella catarrhalis
Pasteurella multocida
Legionella spp.
Anaerobic microorganisms
Clostridium spp., other than *C. difficile*
Other microorganisms
Mycoplasma pneumoniae
Chlamydia trachomatis
Clamydophila pneumoniae
Clamydophilapsitacci
Mycobacterium spp.
Species for which acquired resistance may be a problem#
Aerobic, Gram-positive microorganisms
Streptococcus group A*, C, G
Streptococcus group B
Streptococcus viridans
Enterococcus spp+
Staphylococcus aureus, methicillin-susceptible and methicillin-resistant+
*Streptococcus pneumoniae**+
Staphylococcus epidermidis+
Aerobic, Gram-negative microorganisms
Haemophilus influenzae$
Helicobacter pylori
Anaerobic microorganisms
Bacteroides spp.
Peptococcus/Peptostreptococcus spp.
Inherently resistant microorganisms
Aerobic, Gram-negative microorganisms
Pseudomonas aeruginosa
Acinetobacter
Enterobacteriacea
Anaerobic microorganisms
Fusobacterium spp.
Other microorganisms
Mycobacterium tuberculosis

≥ 10% resistance in at least one country of the European Union

* Species against efficacy has been demonstrated in clinical investigations (if susceptible)

+ Indicates species for which a high rate of resistance (i.e., greater than 50%) have been observed in one or more area/country/region(s) of the EU

§ Breakpoints for macrolides and related antibiotics were set to categorize wild type *H. influenzae* as intermediate

Other information:

Susceptibility and resistance of Streptococcus pneumoniae and Streptococcus spp. to clarithromycin can be predicted by testing erythromycin.

Most available clinical experience from controlled randomized clinical trials indicate that clarithromycin 500 mg twice daily in combination with another antibiotic e.g., amoxicillin or metronidazole and e.g., omeprazole (given at approved levels) for 7 days achieve > 80% H. pylori eradication rate in patients with gastro-duodenal ulcers. As expected, significantly lower eradication rates were observed in patients with baseline metronidazole-resistant H. pylori isolates. Hence, local information on the prevalence of resistance and local therapeutic guidelines should be taken into account in the choice of an appropriate combination regimen for H. pylori eradication therapy. Furthermore, in patients with persistent infection, potential development of secondary resistance (in patients with primary susceptible strains) to an antimicrobial agent should be taken into the considerations for a new retreatment regimen.

Pharmacokinetic properties

Absorption:

Clarithromycin is rapidly and well absorbed from the gastrointestinal tract – primarily in the jejunum – but undergoes extensive first-pass metabolism after oral administration. The absolute bioavailability of a 250-mg clarithromycin tablet is approximately 50%. Food slightly delays the absorption but does not affect the extent of bioavailability. Therefore, clarithromycin tablets may be given without regard to food. Due to its chemical structure (6-O-Methylerythromycin) clarithromycin is quite resistant to degradation by stomach acid. Peak plasma levels of 1 – 2 µg/ml clarithromycin were observed in adults after oral administration of 250 mg twice daily. After administration of 500 mg clarithromycin twice daily the peak plasma level was 2.8 µg/ml. After administration of 250 mg clarithromycin twice daily the microbiologically active 14-hydroxy metabolite attains peak plasma concentrations of 0.6 µg/ml. Steady state is attained within 2 days of dosing.

Distribution:

Clarithromycin penetrates well into different compartments with an estimated volume of distribution of 200-400 l. Clarithromycin provides concentrations in some tissues that are several times higher than the circulating drug levels. Increased levels have been found in both tonsils and lung tissue. Clarithromycin also penetrates the gastric mucus.
Clarithromycin is approximately 70% bound to plasma proteins at therapeutic levels.
Biotransformation and elimination:
Clarithromycin is rapidly and extensively metabolized in the liver. Metabolism is in the liver involving the P450 cytochrome system. Three metabolites are described: N-demethyl clarithromycin, decladinosyl clarithromycin and 14-hydroxy clarithromycin. The pharmacokinetics of clarithromycin is non-linear due to saturation of hepatic metabolism at high doses. Elimination half-life increased from 2-4 hours following administration of 250 mg clarithromycin twice daily to 5 hours following administration of 500 mg clarithromycin twice daily. The half-life of the active 14-hydroxy metabolite ranges between 5 to 6 hours following administration of 250 mg clarithromycin twice daily.
Approximately 20 -40% of clarithromycin is excreted as the unchanged active substance in the urine. This proportion is increased when the dose is increased. An additional 10% to 15% is excreted in the urine as 14-hydroxy metabolite. The rest is excreted in the feces. Renal insufficiency increases clarithromycin levels in plasma, if the dose is not decreased. Total plasma clearance has been estimated to approximately 700 mL/min (11,7 mL/s), with a renal clearance of approximately 170 mL/min (2,8 mL/s).
Special populations:
Renal impairment: Reduced renal insufficiency function results in increased plasma levels of clarithromycin and the active metabolite levels in plasma.

Summary of Clinical Studies

Mycobacterial Infections
Prophylaxis of Mycobacterial Infections

A randomized, double-blind clinical trial (trial 3) compared clarithromycin 500 mg twice a day to placebo in patients with CDC-defined AIDS and CD4 counts less than 100 cells/µL. This trial accrued 682 patients from November 1992 to January 1994, with a median CD4 cell count at entry of 30 cells/mcL. Median duration of clarithromycin was 10.6 months vs. 8.2 months for placebo. More patients in the placebo arm than the clarithromycin arm discontinued prematurely from the trial (75.6% and 67.4%, respectively). However, if premature discontinuations due to *Mycobacterium avium* complex (MAC) or death are excluded, approximately equal percentages of patients on each arm (54.8%) on clarithromycin and 52.5% on placebo) discontinued study drug early for other reasons. The trial was designed to evaluate the following endpoints:

1. MAC bacteremia, defined as at least one positive culture for *Mycobacterium avium* complex bacteria from blood or another normally sterile site
2. Survival
3. Clinically significant disseminated MAC disease, defined as MAC bacteremia accompanied by signs or symptoms of serious MAC infection, including fever, night sweats, weight loss, anemia, or elevations in liver function tests

MAC Bacteremia
In patients randomized to clarithromycin, the risk of MAC bacteremia was reduced by 69% compared to placebo. The difference between groups was statistically significant ($p < 0.001$). On an intent-to-treat basis, the one-year cumulative incidence of MAC bacteremia was 5.0% for patients randomized to clarithromycin and 19.4% for patients randomized to placebo. While only 19 of the 341 patients randomized to clarithromycin developed MAC, 11 of these cases were resistant to clarithromycin. The patients with resistant MAC bacteremia had a median baseline CD4 count of 10 cells/mm3 (range 2 cells/mm3 to 25 cells/mm3). Information regarding the clinical course and response to treatment of the patients with resistant MAC bacteremia is limited. The 8 patients who received clarithromycin and developed susceptible MAC bacteremia had a median baseline CD4 count of 25 cells/mm3 (range 10 cells/mm3 to 80 cells/mm3). Comparatively, 53 of the 341 placebo patients developed MAC; none of these isolates were resistant to clarithromycin. The median baseline CD4 count was 15 cells/mm3 (range 2 cells/mm3 to 130 cells/mm3) for placebo patients that developed MAC.

Survival
A statistically significant survival benefit of clarithromycin compared to placebo was observed (see Figure 3 and Table). Since the analysis at 18 months includes patients no longer receiving prophylaxis the survival benefit of clarithromycin may be underestimated.

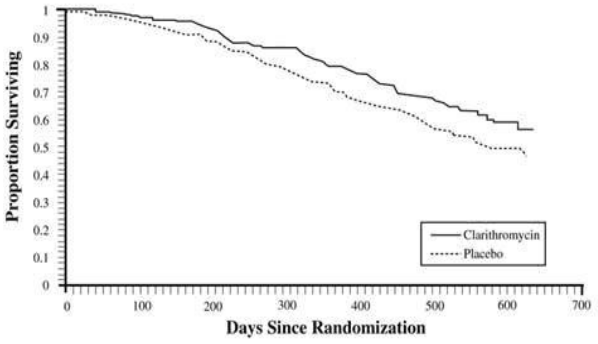

Figure 3. Survival of All Randomized AIDS Patients Over Time in Trial 3

Table. Mortality Rates at 18 months in Trial 3

	Mortality Rates		Reduction in Mortality Rates on Clarithromycin
	Placebo	Clarithromycin	
6 month	9.4%	6.5%	31%
12 month	29.7%	20.5%	31%
18 month	46.4%	37.5%	20%

Clinically Significant Disseminated MAC Disease
In association with the decreased incidence of MAC bacteremia, patients in the group randomized to clarithromycin showed reductions in the signs and symptoms of disseminated MAC disease, including fever, night sweats, weight loss, and anemia.

Treatment of Mycobacterial Infections

Dose-Ranging Monotherapy Trials in Adult AIDS Patients with MAC
Two randomized clinical trials (Trials 1 and 2) compared different dosages of clarithromycin in patients with CDC-defined AIDS and CD4 counts less than100 cells/mcL. These trials accrued patients from May 1991 to March 1992. Trial 500 was a randomized, double-blind trial; trial 577 was an open-label compassionate use trial. Both trials used 500 mg and 1000 mg twice daily dosing of clarithromycin; trial 1 also had a 2000 mg twice daily clarithromycin group. Trial 1 enrolled 154 adult patients and trial 2 enrolled 469 adult patients. The majority of patients had CD4 cell counts less than 50 cells/mcL at study entry. The trials were designed to evaluate the following end points:

1. Change in MAC bacteremia or blood cultures negative for *M. avium*.
2. Change in clinical signs and symptoms of MAC infection including one or more of the following: fever, night sweats, weight loss, diarrhea, splenomegaly, and hepatomegaly.

The results for trial 1 are described below. The trial 2 results were similar to the results of trial 1.

MAC Bacteremia

Decreases in MAC bacteremia or negative blood cultures were seen in the majority of patients in all clarithromycin dosage groups. The mean reductions in MAC colony forming units (CFU) from baseline after 4 weeks of therapy in the 1000 mg (n=32) twice daily and 2000 mg (n=26) twice daily regimen was 2.3 Log CFU compared to 1.5 Log CFU in the clarithromycin 500 mg twice daily (n=35) regimen. A separate trial with a four-drug regimen2 (ciprofloxacin, ethambutol, rifampicin, and clofazimine) had a mean reduction of 1.4 Log CFU.

Clinical outcomes evaluated with the different dosing regimens of clarithromycin monotherapy are shown in Table. The 1000 mg and 2000 mg twice daily doses showed significantly better control of bacteremia during the first four weeks of therapy. No significant differences were seen beyond that point. All of the isolates had MIC less than 8 mcg/mL at pre-treatment. Relapse was almost always accompanied by an increase in MIC.

Table. Outcome with the Different Dosing Regimens of Clarithromycin

Outcome	Clarithromycin 500 mg twice daily	Clarithromycin 1000 mg twice daily	Clarithromycin 2000 mg twice daily
One or more negative blood cultures at any time during acute therapy	61% (30/49)	59% (29/49)	52% (25/48)
Two or more negative blood cultures during acute therapy sustained through study day 84	25% (12/49)	25% (12/49)	8% (4/48)
Death or discontinuation by day 84	23% (11/49)	37% (18/49)	56% (27/48)
Relapse by day 84	14% (7/49)	12% (6/49)	13% (6/48)
Median time to first negative culture (in days)	54	41	29
Median time to first decrease of at least 1 log CFU (in days)	29	16	15
Median time to first positive culture or study discontinuation following the first negative culture (in days)	43	59	43

Clinically Significant Disseminated MAC Disease

Among patients experiencing night sweats prior to therapy, 84% showed resolution or improvement at some point during the 12 weeks of clarithromycin at 500 mg to 2000 mg twice daily doses. Similarly, 77% of patients reported resolution or improvement in fevers at some point. Response rates for clinical signs of MAC are given in Table 15 below.

The median duration of response, defined as improvement or resolution of clinical signs and symptoms, was 2 weeks to 6 weeks.

Since the trial was not designed to determine the benefit of monotherapy beyond 12 weeks, the duration of response may be underestimated for the 25% to 33% of patients who continued to show clinical response after 12 weeks.

Table. Response Rates for Clinical Signs of MAC During 6 Weeks to 12 Weeks of Treatment

Resolution of Fever			Resolution of Night Sweats		
Clarithromycin twice daily dose (mg)	% ever afebrile	% afebrile 6 weeks or more	Clarithromycin twice daily dose (mg)	% ever resolving	% resolving 6 weeks or more
500	67%	23%	500	85%	42%
1000	67%	12%	1000	70%	33%
2000	62%	22%	2000	72%	36%

Weight Gain Greater Than 3%			Hemoglobin Increase Greater Than 1 gm		
Clarithromycin twice daily dose (mg)	% ever gaining	% gaining 6 weeks or more	Clarithromycin twice daily dose (mg)	% ever increasing	% increasing 6 weeks or more
500	33%	14%	500	58%	26%
1000	26%	17%	1000	37%	6%
2000	26%	12%	2000	62%	18%

Survival

Median survival time from trial entry (trial 1) was 249 days at the 500 mg twice daily dose compared to 215 days with the 1000 mg twice daily dose. However, during the first 12 weeks of therapy, there were 2 deaths in 53 patients in the 500 mg twice daily group versus 13 deaths in 51 patients in the 1000 mg twice daily group. The reason for this apparent mortality difference is not known. Survival in the two groups was similar beyond 12 weeks. The median survival times for these dosages were similar to recent historical controls with MAC when treated with combination therapies.2
Median survival time from entry in trial 2 was 199 days for the 500 mg twice a day dose and 179 days for the 1000 mg twice a day dose. During the first four weeks of therapy, while patients were maintained on their originally assigned dose, there were 11 deaths in 255 patients taking 500 mg twice daily and 18 deaths in 214 patients taking 1000 mg twice daily.

Dosage-Ranging Monotherapy Trials in Pediatric AIDS Patients with MAC
Trial 4 was a pediatric trial of 3.75 mg/kg, 7.5 mg/kg, and 15 mg/kg of clarithromycin twice daily in patients with CDC-defined AIDS and CD4 counts less than 100 cells/mcL. The trial enrolled 25 patients between the ages of 1 to 20. The trial evaluated the same endpoints as in the adult trials 1 and 2. Results with the 7.5 mg/kg twice daily dose in the pediatric trial were comparable to those for the 500 mg twice daily regimen in the adult trials.

Combination Therapy in AIDS Patients with Disseminated MAC
Trial 5 compared the safety and efficacy of clarithromycin in combination with ethambutol versus clarithromycin in combination with ethambutol and clofazimine for the treatment of disseminated MAC (dMAC) infection. This 24-week trial enrolled 106 patients with AIDS and dMAC, with 55 patients randomized to receive clarithromycin and ethambutol, and 51 patients randomized to receive clarithromycin, ethambutol, and clofazime. Baseline characteristics between treatment arms were similar with the exception of median CFU counts being at least 1 log higher in the clarithromycin, ethambutol, and clofazime arm.

Compared to prior experience with clarithromycin monotherapy, the two-drug regimen of clarithromycin and ethambutol extended the time to microbiologic relapse, largely through suppressing the emergence of clarithromycin resistant strains. However, the addition of clofazimine to the regimen added no additional microbiologic or clinical benefit. Tolerability of both multidrug regimens was comparable with the most common adverse events being gastrointestinal in nature. Patients receiving the clofazimine-containing regimen had reduced survival rates; however, their baseline mycobacterial colony counts were higher. The results of this trial support the addition of ethambutol to clarithromycin for the treatment of initial dMAC infections but do not support adding clofazimine as a third agent.

14.2 Otitis Media

Otitis Media Trial of Clarithromycin vs. Oral Cephalosporin

In a controlled clinical trial of pediatric patients with acute otitis media performed in the United States, where significant rates of beta-lactamase producing organisms were found, clarithromycin was compared to an oral cephalosporin. In this trial, strict evaluability criteria were used to determine clinical response. For the 223 patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the post-therapy visit was 88% for clarithromycin and 91% for the cephalosporin.

In a smaller number of patients, microbiologic determinations were made at the pre-treatment visit. The presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) are shown in Table.

Table. Clinical Success Rates of Otitis Media Treatment by Pathogen

Pathogen	Clinical Success Rates	
	Clarithromycin	Oral Cephalosporin
S. pneumoniae	13/15 (87%)	4/5
*H. influenzae*a	10/14 (71%)	3/4
M. catarrhalis	4/5	1/1
S. pyogenes	3/3	0/1
All Pathogens Combined	30/37 (81%)	8/11 (73%)
a None of the *H. influenzae* isolated pre-treatment was resistant to clarithromycin; 6% were resistant to the control agent.		

Otitis Media Trials of Clarithromycin vs. Antimicrobial/Beta-lactamase Inhibitor

In two other controlled clinical trials of acute otitis media performed in the United States, where significant rates of beta-lactamase producing organisms were found, clarithromycin was compared to an oral antimicrobial agent that contained a specific beta-lactamase inhibitor. In these trials, strict evaluability criteria were used to determine the clinical responses. In the 233 patients who were evaluated for clinical efficacy, the combined clinical success rate (i.e., cure and improvement) at the post-therapy visit was 91% for both clarithromycin and the control.

For the patients who had microbiologic determinations at the pre-treatment visit, the presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) are shown in Table.

Table. Clinical Success Rates of Acute Otitis Media Treatment by Pathogen

Clinical Success Rates		
PATHOGEN	**Clarithromycin**	**Antimicrobial/Beta-lactamase Inhibitor**
S. pneumoniae	43/51 (84%)	55/56 (98%)
*H. influenzae*a	36/45 (80%)	31/33 (94%)
M. catarrhalis	9/10 (90%)	6/6
S. pyogenes	3/3	5/5
All Pathogens Combined	91/109 (83%)	97/100 (97%)
a Of the *H. influenzae* isolated pre-treatment, 3% were resistant to clarithromycin and 10% were resistant to the control agent.		

14.3 *H. pylori* Eradication to Decrease the Risk of Duodenal Ulcer Recurrence

Clarithromycin + Lansoprazole and Amoxicillin

Two U.S. randomized, double-blind clinical trials (trial 6 and trial 7) in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an active ulcer within one year) evaluated the efficacy of clarithromycin 500 mg twice daily in combination with lansoprazole 30 mg twice daily and amoxicillin 1 gm twice daily as 14-day triple therapy for eradication of *H. pylori*.

H. pylori eradication was defined as two negative tests (culture and histology) at 4 weeks to 6 weeks following the end of treatment.

The combination of clarithromycin plus lansoprazole and amoxicillin as triple therapy was effective in eradication of *H. pylori* (see results in Table 18). Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

A randomized, double-blind clinical trial (trial 8) performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) compared the efficacy of clarithromycin in combination with lansoprazole and amoxicillin as triple therapy for 10 days and 14 days. This trial established that the 10-day triple therapy was equivalent to the 14-day triple therapy in eradicating *H. pylori* (see results in Table 18).

Table. *H. pylori* Eradication Rates-Triple Therapy (clarithromycin/lansoprazole/amoxicillin) Percent of Patients Cured [95% Confidence Interval] (number of patients)

Trial	**Duration**	**Triple Therapy Evaluable Analysisa**	**Triple Therapy Intent-to-Treat Analysisb**
Trial 6	14 days	92c [80 to 97.7] (n = 48)	86c [73.3 to 93.5] (n = 55)
Trial 7	14 days	86d [75.7 to 93.6] (n = 66)	83d [72 to 90.8] (n = 70)
Trial 8e	14 days	85 [77 to 91] (N = 113)	82 [73.9 to 88.1] (N = 126)
	10 days	84 [76 to 89.8] (N = 123)	81 [73.9 to 87.6] (N = 135)

a Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest (Delta West LTD., Bentley, Australia), histology, and/or culture. Patients were included in the analysis if they completed the trial. Additionally, if patients were dropped out of the trial due to an adverse reaction related to the drug, they were included in the analysis as evaluable failures of therapy.
b Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of therapy.
c ($p < 0.05$) versus clarithromycin/lansoprazole and lansoprazole/amoxicillin dual therapy.
d ($p < 0.05$) versus clarithromycin/amoxicillin dual therapy.
e The 95% confidence interval for the difference in eradication rates, 10-day minus 14-day, is (-10.5, 8.1) in the evaluable analysis and (-9.7, 9.1) in the intent-to-treat analysis.

Clarithromycin + Omeprazole and Amoxicillin Therapy

Three U.S., randomized, double-blind clinical trials in patients with *H. pylori* infection and duodenal ulcer disease (n = 558) compared clarithromycin plus omeprazole and amoxicillin to clarithromycin plus amoxicillin. Two trials (trials 9 and 10) were conducted in patients with an active duodenal ulcer, and the third trial (trial 11) was conducted in patients with a duodenal ulcer in the past 5 years, but without an ulcer present at the time of enrollment. The dosage regimen in the trials was clarithromycin 500 mg twice a day plus omeprazole 20 mg twice a day plus amoxicillin 1 gram twice a day for 10 days. In trials 9 and 10, patients who took the omeprazole regimen also received an additional 18 days of omeprazole 20 mg once a day. Endpoints studied were eradication of *H. pylori* and duodenal ulcer healing (trials 9 and 10 only). *H. pylori* status was determined by CLOtest®, histology, and culture in all three trials. For a given patient, *H. pylori* was considered eradicated if at least two of these tests were negative, and none was positive. The combination of clarithromycin plus omeprazole and amoxicillin was effective in eradicating *H. pylori* (see results in Table).

Table. *H. pylori* Eradication Rates: % of Patients Cured [95% Confidence Interval]

	Clarithromycin + omeprazole + amoxicillin		**Clarithromycin + amoxicillin**	
	Per-Protocola	**Intent-to-Treatb**	**Per-Protocola**	**Intent-to-Treatb**
Trial 9	c77 [64, 86] (n = 64)	69 [57, 79] (n = 80)	43 [31, 56] (n = 67)	37 [27, 48] (n = 84)
Trial 10	c78 [67, 88] (n = 65)	73 [61, 82] (n = 77)	41 [29, 54] (n = 68)	36 [26, 47] (n = 84)
Trial 11	c90 [80, 96] (n = 69)	83 [74, 91] (n = 84)	33 [24, 44] (n = 93)	32 [23, 42] (n = 99)

a Patients were included in the analysis if they had confirmed duodenal ulcer disease (active ulcer trials 9 and 10; history of ulcer within 5 years, trial 11) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology, and/or culture. Patients were included in the analysis if they completed the trial. Additionally, if patients dropped out of the trial due to an adverse reaction related to the study drug, they were included in the analysis as failures of therapy. The impact of eradication on ulcer recurrence has not been assessed in patients with a past history of ulcer.
b Patients were included in the analysis if they had documented *H. pylori* infection at baseline and had confirmed duodenal ulcer disease. All dropouts were included as failures of therapy.
c $p < 0.05$ versus clarithromycin plus amoxicillin.

Clarithromycin + Omeprazole Therapy

Four randomized, double-blind, multi-center trials (trials 12, 13, 14, and 15) evaluated clarithromycin 500 mg three times a day plus omeprazole 40 mg once a day for 14 days, followed by omeprazole 20 mg once a day (trials 12, 13, and 15) or by omeprazole 40 mg once a day (trial 14) for an additional 14 days in patients with active duodenal ulcer associated with *H. pylori*. Trials 12 and 13 were conducted in the U.S. and Canada and enrolled 242 and 256 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 219 patients in trial 12 and 228 patients in trial 13. These trials compared the combination regimen to omeprazole and clarithromycin monotherapies. Trials 14 and 15 were conducted in Europe and enrolled 154 and 215 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 148 patients in trial 14 and 208 patients in trial 15. These trials compared the combination regimen to omeprazole monotherapy. The results for the efficacy analyses for these trials are described in Tables below.

Duodenal Ulcer Healing

The combination of clarithromycin and omeprazole was as effective as omeprazole alone for healing duodenal ulcer (see Table 20).

Table. End-of-Treatment Ulcer Healing Rates Percent of Patients Healed (n/N)

Trial	**Clarithromycin + Omeprazole**	**Omeprazole**	**Clarithromycin**
U.S. Trials			
Trial 13	94% (58/62)a	88% (60/68)	71% (49/69)
Trial 12	88% (56/64)a	85% (55/65)	64% (44/69)
Non-U.S. Trials			
Trial 15	99% (84/85)	95% (82/86)	N/A
Trial 14b	100% (64/64)	99% (71/72)	N/A

a $p < 0.05$ for clarithromycin + omeprazole versus clarithromycin monotherapy.
b In trial 14 patients received omeprazole 40 mg daily for days 15 to 28.

Eradication of H. pylori Associated with Duodenal Ulcer

The combination of clarithromycin and omeprazole was effective in eradicating *H. pylori*.. *H. pylori* eradication was defined as no positive test (culture or histology) at 4 weeks following the end of treatment, and two negative tests were required to be considered eradicated. In the per-protocol analysis, the following patients were excluded: dropouts, patients with major protocol violations, patients with missing *H. pylori* tests post-treatment, and patients that were not assessed for *H. pylori* eradication at 4 weeks after the end of treatment because they were found to have an unhealed ulcer at the end of treatment.

Table. *H. pylori* Eradication Rates (Per-Protocol Analysis) at 4 to 6 weeks Percent of Patients Cured (n/N)

Trial	Clarithromycin + Omeprazole	Omeprazole	Clarithromycin
U.S. Trials			
Trial 13	64% (39/61)a,b	0% (0/59)	39% (17/44)
Trial 12	74% (39/53)a,b	0% (0/54)	31% (13/42)
Non-U.S. Trials			
Trial 15	74% (64/86)b	1% (1/90)	N/A
Trial 14	83% (50/60)b	1% (1/74)	N/A
a Statistically significantly higher than clarithromycin monotherapy ($p < 0.05$). b Statistically significantly higher than omeprazole monotherapy ($p < 0.05$).			

Duodenal Ulcer Recurrence
Ulcer recurrence at 6-months and at 12 months following the end of treatment was assessed for patients in whom ulcers were healed post-treatment (see the results in Table). Thus, in patients with duodenal ulcer associated with *H. pylori* infection, eradication of *H. pylori* reduced ulcer recurrence.

Table. Duodenal Ulcer Recurrence at 6 months and 12 months in Patients with Healed Ulcers

	***H. pylori* Negative at 4 to 6 Weeks**	***H. pylori* Positive at 4 to 6 Weeks**
U.S. Trials Recurrence at 6 Months		
Trial 100		
Clarithromycin + Omeprazole	6% (2/34)	56% (9/16)
Omeprazole	(0/0)	71% (35/49)
Clarithromycin	12% (2/17)	32% (7/22)
Trial 067		
Clarithromycin + Omeprazole	38% (11/29)	50% (6/12)
Omeprazole	(0/0)	67% (31/46)
Clarithromycin	18% (2/11)	52% (14/27)
Non-U.S. Trials Recurrence at 6 Months		
Trial 058		
Clarithromycin + Omeprazole	6% (3/53)	24% (4/17)
Omeprazole	0% (0/3)	55% (39/71)
Trial 812b		
Clarithromycin + Omeprazole	5% (2/42)	0% (0/7)
Omeprazole	0% (0/1)	54% (32/59)
Non-U.S. Trials Recurrence at 12 Months in Trial 14		
Clarithromycin + Omeprazole	3% (1/40)	0% (0/6)
Omeprazole	0% (0/1)	67% (29/43)

PRECLINICAL SAFETY DATA

In 4-week-studies in animals, toxicity of clarithromycin was found to be related to the dose and to the duration of the treatment. In all species, the first signs of toxicity were observed in the liver, in which lesions were seen within 14 days in dogs and monkeys. The systemic levels of exposure, related to this toxicity, are not known in detail, but toxic doses were clearly higher than the therapeutic doses recommended for humans. Other tissues affected included the stomach, thymus and other lymphoid tissues as well as the kidneys. At near therapeutic doses conjunctival injection and lacrimation occurred only in dogs. At a dose of 400 mg/kg/day some dogs and monkeys developed corneal opacities and/or oedema.
No mutagenic effects were found in *in vitro*- and *in vivo* -studies with clarithromycin
Studies on reproduction toxicity showed that administration of clarithromycin at doses 2x the clinical dose in rabbit (i.v.) and x10 the clinical dose in monkey (p.o.) resulted in an increased incidence of spontaneous abortions. These doses were related to maternal toxicity. No embryotoxicity or teratogenicity was noted in rat studies. Cardiovascular malformations were observed in rats treated with doses of 150 mg/kg/d. In mouse at doses x70 the clinical dose cleft palate occurred at varying incidence (3-30%).
Clarithromycin has been found in the milk of lactating animals.

In 3-day old mice and rats, the LD50 values were approximately half those in adult animals. Juvenile animals presented similar toxicity profiles to mature animals although enhanced nephrotoxicity in neonatal rats has been reported in some studies. Slight reductions in erythrocytes, platelets and leukocytes have also been found in juvenile animals.
Clarithromycin has not been tested for carcinogenicity.

PRESENTATION

Clariza-250mg Tablets are available in pack of 10's

Clariza-500mg Tablets are available in pack of 10's

INSTRUCTIONS

-To be sold on the prescription of a registered medical practitioner only.

-Protect from sunlight, moisture and heat.

-Store below 30°C.

-Keep all medicines out of sight and reach of children.

REGISTRATION NUMBER

Clariza-250mg: 054513

Clariza-500mg: 054514

Manufacturing License No.: 000647

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION – As per registrations letter

Marketed by:

The Searle Company Limited.

32-km, Multan Road, Lahore-Pakistan. Marketed by:

Searle Biosciences (Pvt.) Limited,

First Floor, N.I.C.L. Building, Abbasi Shaheed Road, Karachi - Pakistan.

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