Clarithromycin

Klaz®

125 mg/5 mL & 250 mg/5 mL Granules for Suspension
250 mg & 500 mg Tablets

Klaz® OD

500 mg Extended-Release Tablet

Rx

ANTIBACTERIAL

FORMULATION
After reconstitution, each 5 mL suspension contains:
Clarithromycin ..... 125 mg or 250 mg

Each film-coated tablet contains:
Clarithromycin ..... 250 mg or 500 mg

Each extended-release film-coated tablet contains:
Clarithromycin ..... 500 mg

PRODUCT DESCRIPTION
Clarithromycin (Klaz®) 125 mg/5 mL and 250 mg/5 mL granules for suspension: white to off-white granules containing granular, red-colored strawberry-flavored specks for reconstitution into a pink, slightly viscous suspension with strawberry odor and flavor.

Clarithromycin (Klaz®) 250 mg and 500 mg tablet: yellow, elliptical-shaped film-coated tablet, plain on both sides.

Clarithromycin (Klaz®OD) 500 mg extended-release tablet: yellow, film-coated, oblong-shaped, biconvex tablet with both sides plain.

PHARMACODYNAMICS
Clarithromycin, a semi-synthetic 14-membered ring macrolide, exerts its antibacterial activity by binding to the donor site on the 50s subunit of the bacterial ribosome thus inhibiting protein synthesis. Like other macrolides, clarithromycin penetrates intracellularly and is highly concentrated in the polymorphonuclear leukocytes and tissue macrophages. There is no evidence, however, that clarithromycin has *in vivo* pharmacologic effect on mammalian cells.

ANTIMICROBIAL SPECTRUM OF ACTIVITY
Clarithromycin has demonstrated activity *in vitro* and in clinical infections against most strains of the following microorganisms:

Aerobic Gram-Positive	*Staphylococcus aureus* *Streptococcus pneumoniae* *Streptococcus pyogenes* *Listeria monocytogenes*
Aerobic Gram-Negative	*Haemophilus influenzae* *Haemophilus parainfluenzae* *Moraxella catarrhalis* *Neisseria gonorrhoeae* *Legionella pneumophila*
Mycobacteria	*Mycobacterium leprae* *Mycobacterium kansasii* *Mycobacterium chelonae* *Mycobacterium fortuitum* *Mycobacterium avium* complex (MAC) consisting of: *Mycobacterium avium* *Mycobacterium intracellulare*
Other microorgansims	*Mycoplasma pneumoniae* *Chlamydia pneumoniae* (TW-138; AR-39) *Helicobacter pylori*

Beta-lactamases have no effect on clarithromycin activity.

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

Omeprazole/clarithromycin dual therapy, ranitidine bismuth citrate/clarithromycin dual therapy, omeprazole/clarithromycin/amoxicillin triple therapy and lansoprazole/clarithromycin/amoxicillin triple therapy have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections.

Clarithromycin has demonstrated *in vitro* activity against most strains of the following microorganisms; however, clinical significance is unknown:

Aerobic Gram-Positive	*Streptococcus agalactiae* *Streptococci* (Group C, F, G) Viridans group streptococci
Aerobic Gram-Negative	*Bordetella pertussis* *Legionella pneumophila* *Pasteurella multocida*
Anaerobes	*Clostridium perfringens* *Peptococcus niger* *Propionibacterium acnes* *Prevotella melaninogenica*
Other microorgansims	*Borrelia burgdorferi* *Campylobacter jejuni* *Treponema pallidum*

It is suggested to carry out susceptibility tests.

PHARMACOKINETICS
Film-coated Tablet and Suspension
Clarithromycin is rapidly absorbed and reaches peak serum concentrations approximately 2 hours after oral administration.

Clarithromycin has non-linear, dose-dependent pharmacokinetics due to saturation of metabolic pathways. This nonlinearity is minimal with usual dosages (250 to 500 mg every 8 to 12 hours) but increases disproportionately with single high doses (e.g., 1.2 g) or with multiple clarithromycin doses.

Food delays the onset of clarithromycin absorption and increases peak time (T_{max}) from 2 to 2.5 hours; the extent of absorption is unaffected.

Administration of a 250 mg clarithromycin dose, either as tablet or suspension to fasting healthy adults, results in average peak serum clarithromycin concentration (C_{max}) of 0.6 mcg/mL reached within 1 to 4 hours. After oral administration of clarithromycin 250 mg tablet every 12 hours or clarithromycin 500 mg tablet every 8 to 12 hours, peak steady-state clarithromycin concentrations were achieved within 3 days and averaged about 1 to 2 or 3 to 4 mcg/mL, respectively, while peak steady-state 14-hydroxy (OH) clarithromycin concentrations were achieved within 3 to 4 days and averaged about 0.6 to 1 mcg/mL for both doses. The active metabolite of clarithromycin is 14-hydroxy (OH) clarithromycin.

The overall bioavailability of clarithromycin suspension was equivalent to or slightly greater than the tablet in a single 250 mg dose study in adults. Administration of clarithromycin suspension with food led to a slight delay in the onset of absorption but did not affect the overall bioavailability of clarithromycin. The C_{max} area under the plasma concentration time curve (AUC), and half-life ($t_{1/2}$) for clarithromycin suspension (non-fasted state) were 0.95 mcg/mL, 6.5 mcg hr/mL, and 3.7 hours, respectively, and for clarithromycin tablet (fasted state) were 1.1 mcg/mL, 6.3 mcg.hr/mL, and 3.3 hours, respectively.

In a single-dose study in children under fed conditions, clarithromycin suspension 7.5 mg/kg resulted in an increase in C_{max} from 3.6 ± 1.5 mcg/mL to 4.6 ± 2.8 mcg/mL and the AUC from 10 ± 5.5 mcg.hr/mL to 14.2 ± 9.4 mcg.hr/mL.

In a multiple dose study in adults, administration of clarithromycin suspension 250 mg every 12 hours resulted in steady state after the fifth dose: C_{max} 1.98 mcg/mL, AUC 11.5 mcg.hr/mL, tmax 2.8 hours and $t_{1/2}$ 3.2 hours for clarithromycin, and 0.67 mcg/mL, 5.33 mcg hr/mL, 2.9 hours and 4.9 hours, respectively, for 14-OH clarithromycin. When a similar formulation was administered in children requiring oral antibiotic treatment, steady-state pharmacokinetic parameters reached after the ninth dose on treatment day 5 were: Cmax 4.6 mcg/mL, AUC 15.7 mcg.hr/mL, t_{max} 2.8 hours and $t_{1/2}$ 2.2 hours for clarithromycin, and 1.64 mcg/mL, 6.69 mcg.hr/mL, 2.7 hours and 4.3 hours, respectively, for 14-OH clarithromycin.

Data on the penetration of clarithromycin into the middle ear fluid in patients with secretory otitis media were obtained in a study in children receiving clarithromycin 7.5 mg/kg every 12 hours. The mean concentrations of clarithromycin and 14-OH clarithromycin in the middle ear fluid were 2.53 mcg/mL and 1.27 mcg/mL, respectively. These concentrations were generally twice as high as the corresponding concentrations in serum (i.e., 1.7 mcg/mL for clarithromycin and 0.8 mcg/mL for 14-OH clarithromycin).

Clarithromycin and 14-OH clarithromycin are distributed into most body tissues and fluids including lung, tonsil and nasal tissues. Tissue concentrations are higher than serum concentrations because of the drug's high intracellular concentrations. Clarithromycin is also distributed into the cerebrospinal fluid after oral administration but there is no evidence regarding its use in the treatment of meningitis.

At usual therapeutic concentrations, clarithromycin's protein binding is approximately 42% to 72%. It has a high affinity for α_1-glycoprotein.

Clarithromycin's $t_{1/2}$ after a 250 mg dose as conventional tablet given twice a day is about 3 to 4 hours; the $t_{1/2}$ is 5 to 7 hours with 500 mg twice a day. The elimination $t_{1/2}$ at steady-state is similar with equivalent clarithromycin doses as tablet or oral suspension. The $t_{1/2}$ of clarithromycin ER tablet was 6.64 hours.

Clarithromycin is metabolized primarily in the liver via the cytochrome P450 3A (CYP3A) isoenzyme. Although seven metabolites of clarithromycin have been identified, 14-OH clarithromycin is the principal metabolite in the serum and is the only one with substantial antibacterial activity.

About 20-30%, or 40% of a given clarithromycin dose is excreted unchanged in the urine within 12 hours after administration of clarithromycin 250 mg or 500 mg tablet, or 250 mg (125 mg/5 mL) suspension every 12 hours, respectively. Urinary excretion of clarithromycin ER accounts for about 40% of the clarithromycin dose. Fecal elimination accounts for approximately 30%.

Extended-release Tablet
Administration of clarithromycin extended-release (ER) tablets provides extended absorption of clarithromycin from the gastrointestinal (GI) tract. Although the 24-hour AUCs for clarithromycin and 14-OH clarithromycin following administration of clarithromycin ER tablets are equivalent to the 24-hour AUCs of an equal total daily dose as clarithromycin tablets, clarithromycin ER tablets result in lower and later C_{max} of clarithromycin and 14-OH clarithromycin. While the extent of formation of 14-OH clarithromycin following oral administration of clarithromycin 500 mg ER tablets is not affected by food, administration under fasting conditions is associated with approximately 30% lower clarithromycin AUC. Therefore, clarithromycin ER tablets should be taken with meals.

In healthy human subjects under fed conditions, the mean C_{max} of 1.797 mcg/mL was achieved 5.58 hours ($t_{(max)}$) following oral administration of clarithromycin 500 mg ER tablet once a day for five consecutive days. The AUC (0-τ) was 20.406 mcg.hr/mL and the AUC(0-∞) was 22.214 mcg.hr/mL.

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INDICATION
For the treatment of the following infections caused by susceptible microorganisms:

- Upper respiratory tract infections including streptococcal pharyngitis and tonsillitis, acute maxillary sinusitis, and acute otitis media
- Lower respiratory tract infections including bronchitis and pneumonia
- Uncomplicated skin and skin structure infections including impetigo, folliculitis, cellulitis, abscesses (usually require surgical drainage)
- Disseminated or localized mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare*. Localized infections due to *Mycobacterium kansasii, Mycobacterium chelonae* and *Mycobacterium fortuitum* (usually in combination with other antimicrobial agents)
- *Helicobacter pylori* infections (in combination with other drugs)
- Odontogenic infections

Prevention of disseminated *Mycobacterium avium* complex (MAC) infection in patients with advanced HIV infection.

Note: *Clarithromycin ER tablet is indicated only for the treatment of adults with upper and lower respiratory tract infections and skin structure infections. The efficacy and safety of clarithromycin ER tablets in treating other infections have not been established.*

DOSAGE AND MODE OF ADMINISTRATION

CLARITHROMYCIN (KLAZ®) TABLET

Usual Adult Dose: 250 mg to 500 mg (with or without food) every 12 hours for 5 to 14 days.
In Children ≥ 12 years old (who can swallow tablet whole): Follow adult dosing

Indication	CLARITHROMYCIN (KLAZ®) TABLET	
	Recommended Oral Adult Dose	Duration of Treatment
Pharyngitis/tonsillitis	250 mg every 12 hours	10 days
Acute maxillary sinusitis	500 mg every 12 hours	7 to 14 days
Acute exacerbation of chronic bronchitis	250 mg to 500 mg every 12 hours	7 to 14 days
Community-acquired pneumonia	250 mg to 500 mg every 12 hours	7 to 14 days
Uncomplicated skin and skin structure infections	250 mg every 12 hours	7 to 14 days
Odontogenic infections	250 mg every 12 hours	5 days
Treatment of disseminated or localized mycobacterial infections *	500 mg every 12 hours	Treatment of MAC infections in AIDS patients should be continued for as long as clinical and mycobacterial improvements are observed.
Prevention of disseminated MAC infection in patients with advanced HIV infection	500 mg every 12 hours	Treatment should be continued while CD_4 count is less than 100/mm^3
Helicobacter pylori infections	**Triple therapy regimen:** Clarithromycin 500 mg plus amoxicillin 1000 mg plus omeprazole 20 mg (all twice a day)	7 to 10 days *(in patients with an ulcer present at the time of initiation of treatment, an additional 18 days of omeprazole 20 mg once a day is recommended for ulcer healing and symptom relief)*
	Dual therapy regimen: Clarithromycin 500 mg three times a day plus omeprazole 40 mg once a day	14 days (followed by omeprazole 20 mg or 40 mg once a day for an additional 14 days)

**Clarithromycin should be used in combination with other antimycobacterial drugs.*

CLARITHROMYCIN EXTENDED-RELEASE (KLAZ® OD) TABLET
Clarithromycin ER (KLAZ® OD) tablet should be taken with food and should be swallowed whole and not chewed, broken or crushed.

Usual Adult Dose: 500 mg once a day
In more severe infections, the dosage may be increased to 1000 mg (2 x 500 mg) once a day. The usual duration of treatment is 5 to 14 days.

In Children ≥ 12 years old (who can swallow tablet whole): Follow adult dosing

CLARITHROMYCIN (KLAZ®) SUSPENSION
Clarithromycin suspension may be given with or without food, or with milk.

Indication	CLARITHROMYCIN (KLAZ®) SUSPENSION	
	Recommended Oral Pediatric Dose	Duration of Treatment
Non-mycobacterial infections	**Usual Pediatric Dose:** 15 mg/kg body weight/day to be given in two divided doses every 12 hours (Maximum dose: 1000 mg/day) **Age Group** / **Recommended Clarithromycin dose every 12 hours**: 125 mg/ 5mL: 6 months to 1 year: 2.5 mL (½ teaspoonful); 2 to 6 years: 5 mL (1 teaspoonful); 7 to 12 years: 7.5 to 10 mL (1 ½ to 2 teaspoonsful); 250 mg/ 5mL: 6 months to 1 year: 1.25 mL; 2 to 6 years: 2.5 mL (½ teaspoonful); 7 to 12 years: 5 mL (1 teaspoonful)	5 to 10 days, depending on the type and severity of infection. Treatment of streptococcal pharyngitis should be 10 days.
Treatment of disseminated or localized mycobacterial infections*	7.5 mg/kg body weight (not exceeding 500 mg) to be given every 12 hours	Treatment of MAC infections in AIDS patients should be continued for as long as clinical and mycobacterial improvements are observed.
Prevention of disseminated MAC infection in patients with advanced HIV infection	7.5 mg/kg body weight (not exceeding 500 mg) to be given every 12 hours *(The doses recommended are derived from MAC treatment studies in children.)*	Treatment should be continued while CD_4 count is less than 100/mm^3

**Clarithromycin should be used in combination with other antimycobacterial drugs.*

Directions for Reconstitution

Clarithromycin (Klaz®) 125 mg/5 mL or 250 mg/5 mL Granules for Suspension pack size	Volume of distilled water to be added	Directions
35 mL	19.8 mL	Tap the bottle several times to loosen the granules before reconstitution. Add the required amount of distilled water in two portions and shake vigorously until all contents are evenly suspended.
70 mL	39.6 mL	
Protect from light. Store at room temperature and use within 14 days once reconstituted. Shake well before taking each dose. Discard any unused portion after 14 days. DO NOT REFRIGERATE.		

Dosage in Patients with Renal Impairment (with creatinine clearance < 30 mL/min):

Adult Patients	Pediatric Patients
Clarithromycin dosage should be reduced by one-half, i.e., 250 mg once a day, **OR** 250 mg every 12 hours in more severe infections.	Clarithromycin dosage should be reduced by one-half, i.e., up to a maximum of 250 mg once a day, **OR** up to a maximum of 250 mg every 12 hours in more severe infections.

- Dosage should not be continued beyond 14 days in these patients.
- The safety and efficacy of 500 mg clarithromycin in patients with severe renal impairment have not been established.
- Clarithromycin ER tablets should not be used in these patients since the dose of clarithromycin ER cannot be reduced from 500 mg once a day.

Dosage in Patients with Hepatic Impairment: No dosage adjustment necessary.
Or, as prescribed by a physician.

CONTRAINDICATIONS
- Known hypersensitivity to clarithromycin, erythromycin or any macrolide antibiotic, or to any component of the product
- Patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of clarithromycin
- Patients with a history of QT prolongation or ventricular cardiac arrhythmia, including *torsades de pointes*
- Concomitant administration with cisapride, pimozide, astemizole, terfenadine and ergotamine or dihydroergotamine which may result in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and *torsades de pointes*) leading to death
- Concomitant administration with simvastatin or lovastatin
- Concomitant administration of clarithromycin and colchicine in patients with renal or hepatic impairment
- Clarithromycin ER tablet is contraindicated in patients with creatinine clearance <30 mL/min

WARNINGS AND PRECAUTIONS

Clarithromycin should not be used in pregnant women except where no alternative therapy is appropriate, particularly during the first trimester of pregnancy. If the patient becomes pregnant while receiving clarithromycin, the patient should be informed of the potential hazard to the fetus (see **STATEMENT ON USAGE FOR HIGH RISK GROUPS**).

The concomitant use of clarithromycin and drugs metabolized by CYP3A and/or transported by P-glycoprotein (P-gp) may result in significant safety concerns (see **INTERACTIONS WITH OTHER MEDICAMENTS**).

Use in Pregnancy: **Clarithromycin has been associated with adverse effects of pregnancy outcome and/or embryo-fetal development in animals at doses that produced plasma levels 2 to 17 times those achieved with the maximum recommended human doses (see STATEMENT ON USAGE FOR HIGH RISK GROUPS).**

Acute Hypersensitivity Reactions: In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) [e.g., acute generalized exanthematous pustulosis, Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS)], and Henoch-Schönlein purpura, clarithromycin treatment should be discontinued immediately and appropriate therapy be instituted.

Serious hypersensitivity reactions may require immediate emergency treatment including epinephrine, antihistamines or corticosteroids.

QT Prolongation: Clarithromycin has been associated with QT interval prolongation and infrequent cases of arrhythmia including *torsades de pointes*. Fatalities have been reported. Due to the risk of QT prolongation, clarithromycin should be avoided in patients with ongoing proarrhythmic conditions such as coronary artery disease, uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving class I (quinidine, procainamide) or class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Hepatotoxicity: Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis (with or without jaundice), has been reported with clarithromycin. The hepatic impairment may be severe and is usually reversible. In some cases, hepatic failure resulting in death has been reported and generally has been associated with serious underlying illnesses and/or concomitant medications

Clarithromycin should be discontinued immediately if signs and symptoms of hepatitis occur, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Use of Clarithromycin with Other Drugs

Use of Clarithromycin with other drugs may lead to drug-drug interactions.

Atypical Antipsychotics (quetiapine)

Due to inhibition of CYP3A by clarithromycin, concomitant use of clarithromycin with quetiapine results in increased quetiapine concentrations. Serious and life-threatening adverse reactions, including malignant neuroleptic syndrome, have been reported. Clarithromycin should not be used in combination with quetiapine unless clinically necessary (see **INTERACTIONS WITH OTHER MEDICAMENTS**). Monitoring and dose reductions may be required.

Oral Hypoglycemic Agents/Insulin

The concomitant use of clarithromycin and oral hypoglycemic agents (such as sulfonylureas) and/or insulin can result in significant hypoglycemia. Careful monitoring of glucose is recommended (see **INTERACTIONS WITH OTHER MEDICAMENTS**).

Oral Anticoagulants

There is a risk of serious hemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is concomitantly used with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concomitantly (see **INTERACTIONS WITH OTHER MEDICAMENTS**). NZ, AUS, UK, CANADA

HMG-CoA Reductase Inhibitors

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see **CONTRAINDICATIONS**). Caution should be exercise 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 the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g., fluvastatin) can be considered (see **INTERACTIONS WITH OTHER MEDICAMENTS**).

Triazolobenzodiazepines and Related Benzodiazepines

Caution is advised regarding the concomitant administration of clarithromycin with triazolobenzodiazepines (such as triazolam and alprazolam), or with other benzodiazepines (such as intravenous midazolam) due to increased risk of central nervous system (CNS) effects (e.g., somnolence and confusion) (see **INTERACTIONS WITH OTHER MEDICAMENTS**).

Calcium Channel Blockers

Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem, nifedipine) due to risk of hypotension and acute kidney injury. Most reports of acute kidney injury with calcium channel blockers metabolized by CYP3A4 involved elderly patients 65 years of age or older. Use clarithromycin with caution when administered concomitantly with medications that induce the cytochrome CYP3A4 enzyme (see **INTERACTIONS WITH OTHER MEDICAMENTS**).

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

All-Cause Mortality in Patients With Coronary Artery Disease 1 to 10 Years After Clarithromycin

In one clinical trial evaluating treatment with clarithromycin on outcomes in patients with coronary artery disease, an increase in risk of all-cause mortality was observed in patients randomized to clarithromycin. Clarithromycin for treatment of coronary artery disease is not an approved indication. The causes of the increased risk has not been established. Other epidemiologic studies evaluating this risk have shown variable results. Consider balancing this potential risk with treatment benefits when prescribing clarithromycin in patients who have suspected or confirmed coronary artery disease.

Clostridium difficile-associated diarrhea (CDAD): This has been reported with the use of nearly all antibacterial agents, including clarithromycin, and may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea following administration of antibacterial agents.

Myasthenia Gravis: Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome has been reported in patients receiving clarithromycin.

Patients Infected with Human Immunodeficiency Virus (HIV): Several studies of HIV-positive patients receiving clarithromycin for treatment of MAC infection have shown poorer survival in those patients randomized to receive doses higher than 500 mg twice a day. The explanation for these results has not been determined. Treatment or prophylaxis of MAC infection with clarithromycin should not exceed the approved dose of 500 mg twice a day.

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.

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

Other Precautions
- Use with caution in patients receiving other ototoxic drugs, especially aminoglycosides. Monitoring of vestibular and auditory function should be carried out during and after treatment.
- There is a possibility of cross resistance between clarithromycin and other macrolides, as well as lincomycin and clindamycin.
- For the eradication of *Helicobacter pylori*, clarithromycin and amoxicillin should not be administered to patients with renal impairment since the appropriate dosage in this patient population has not yet been established.
- Clarithromycin in combination with ranitidine bismuth citrate should not be used in patients with creatinine clearance <25 mL/minute and in those with a history of acute porphyria.
- Prescribing clarithromycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to be beneficial to the patient and increases the risk of the development of drug-resistant microorganisms.
- As with other antibacterial drugs, long term or repeated use may result in overgrowth of non-susceptible organisms, including fungi. Use of any antimicrobial therapy, such as clarithromycin, to treat *Helicobacter pylori* infection may select for drug-resistant organisms.

Effects on the Ability to Drive and Use Machines

The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

INTERACTIONS WITH OTHER MEDICAMENTS
Potentially Hazardous Interactions

Like erythromycin, concurrent use of clarithromycin with drugs metabolized by the cytochrome P-450 system may be associated with elevated serum levels of these drugs. The table below describes some of these interactions:

DRUGS	NATURE OF INTERACTION
Drugs Metabolized by Hepatic Microsomal Enzymes	
Carbamazepine	Manifestations of carbamazepine toxicity (i.e., drowsiness, dizziness, ataxia) may occur. Reduction in carbamazepine dosage and/or monitoring of carbamazepine levels are recommended.
Cisapride/Pimozide	Cardiac arrhythmias including QT prolongation, ventricular tachycardia, ventricular fibrillation, and *torsades de pointes* which may lead to death have been reported when the drugs are given concomitantly.
Darifenacin	The dosage of darifenacin should not exceed 7.5 mg/day when administered concomitantly with clarithromycin.
Disopyramide	Electrocardiogram and serum disopyramide concentrations should be monitored. Ventricular fibrillation, prolongation of QT interval, and a marked increase in disopyramide elimination t1/2 were reported.
Erlotinib	Use with caution when administered concomitantly with clarithromycin. Erlotinib dosage should be reduced if severe adverse effects occur.
Eszopiclone	Eszopiclone dosage should be reduced if used concomitantly with clarithromycin. In such cases, the initial eszopiclone dosage should not exceed 1 mg but may be increased to 2 mg if clinically indicated.
Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (e.g., atorvastatin, lovastatin, rosuvastatin, simvastatin)	Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated. As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors. Rhabdomyolysis has been reported rarely in patients taking these drugs concomitantly. Patients should be monitored for signs and symptoms of myopathy. Rhabdomyolysis has also been reported rarely in patients taking clarithromycin with atorvastatin or rosuvastatin. When used with clarithromycin, atorvastatin or rosuvastatin should be administered in the lowest possible doses. Therefore, adjustment of the statin dose or use of a statin that is not dependent on CYP3A metabolism (e.g., fluvastatin or pravastatin) should be considered.
Rifampicin, Rifabutin, Rifapentine	Concomitant administration resulted in increased metabolism of clarithromycin. The frequency of uveitis is increased when clarithromycin is given concomitantly with rifabutin.
Terfenadine, Astemizole	Concomitant administration resulted in a 2- to 3-fold increase in the serum level of the acid metabolite of terfenadine and in the prolongation of the QT interval which could lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.
Tolterodine	The primary route of metabolism for tolterodine is via CYP2D6. However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, CYP3A inhibition results in significantly higher serum concentrations of tolterodine. Tolterodine 1 mg twice a day is recommended for patients deficient in CYP2D6 activity (poor metabolizers) when co-administered with clarithromycin.
Atypical Antipsychotics (Quetiapine)	Concomitant administration could result in increased quetiapine exposure and possible quetiapine related toxicities. There have been postmarketing reports of somnolence, orthostatic hypotension, altered state of consciousness, neuroleptic malignant syndrome, and QT prolongation during concomitant use. For other atypical antipsychotic drugs (aripiprazole and risperidone) metabolized by CYP3A4, it is also recommended that concomitant administration with clarithromycin be avoided due to potential pharmacokinetic interactions.
Other drugs affecting hepatic microsomal enzymes	Interactions with erythromycin and/or clarithromycin have been reported with a number of other drugs metabolized by the cytochrome P-450 system (e.g., alfentanil, bromocriptine, cilostazol, hexobarbital ibrutinib, methylprednisolone, phenytoin, sirolimus, valproate, and vinblastine). The metabolism of these drugs may be inhibited by concomitant administration with clarithromycin and may be associated with increased serum levels of these drugs. As with other inducers of CYP3A (e.g., carbamazepine, rifampicin), St. John's wort may induce the metabolism of clarithromycin which may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy.
Anti-retroviral Agents	
Amprenavir	Slightly increased amprenavir concentrations and AUC and possibly decreased clarithromycin concentrations have been noted.
Atazanavir	Increased C_{max} and AUC of clarithromycin, decreased C_{max} and AUC of 14-OH clarithromycin, and increased C_{max} and AUC of atazanavir have been observed. Increased concentrations of clarithromycin may lead to prolongation of QT interval. Clarithromycin dosage should be reduced by 50% in patients receiving atazanavir. In addition, alternative antibiotic therapy should be considered for indications other than MAC infections since the decreased plasma concentrations of 14-OH clarithromycin may adversely affect clarithromycin's efficacy in the treatment of certain infections.
Delavirdine	AUC of clarithromycin is increased by 100%. It is recommended that clarithromycin dose be reduced by 50% in patients with creatinine clearance of 30 to 60 mL/minute and reduced by 75% in patients with creatinine clearance of < 30 mL/minute.
Didanosine	Simultaneous administration of clarithromycin tablets and didanosine to HIV-infected adults resulted in no statistically significant change in didanosine pharmacokinetics.
Efavirenz	Rash has been reported in most patients receiving efavirenz and clarithromycin concurrently; it is recommended that an alternative anti-infective agent be used if such condition occurs.
Etravirine	Clarithromycin exposure was decreased by etravirine; however, concentrations of 14-OH clarithromycin were increased. Since 14-OH clarithromycin has reduced activity against MAC, overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC.
Fosamprenavir	Studies using amprenavir indicate that concomitant use of clarithromycin and fosamprenavir may result in increased amprenavir concentrations and AUC.
Indinavir	Increased indinavir and clarithromycin concentrations have been observed.
Lopinavir	Concomitant use of clarithromycin with the fixed combination of lopinavir and ritonavir may result in increased clarithromycin concentrations. Modification of the usual dosage of clarithromycin is not necessary in patients with normal renal function; however, clarithromycin dosage should be reduced by 50% in patients with creatinine clearances of 30 to 60 mL/min and reduced by 75% in patients with creatinine clearances < 30 mL/minute.
Nevirapine	Plasma concentrations and AUC of clarithromycin is decreased while the plasma concentration and AUC of its metabolite is increased. This leads to reduced activity of clarithromycin, therefore, it is recommended that an alternative anti-infective be used.
Ritonavir	Increased C_{max} and AUC of clarithromycin by 31% and 77%, respectively, and decreased C_{max} and AUC of 14-OH clarithromycin by 99% and 100%, respectively, have been observed. The C_{max} and AUC of ritonavir were also increased by 12% to 15%. It is recommended that clarithromycin dose be reduced by 50% in patients with creatinine clearance of 30 to 60 mL/minute and reduced by 75% in patients with creatinine clearance of < 30 mL/minute.
Saquinavir	Increased plasma concentrations of both drugs have been noted.
Zidovudine	Simultaneous administration may result in decreased steady-state zidovudine concentrations. Administration of clarithromycin (tablets or suspension) and zidovudine should be separated by at least two hours. The impact of co-administration of clarithromycin ER tablets and zidovudine has not been evaluated.
Other Medicinal Products	
Anticoagulant (e.g., warfarin)	There have been reports of increased anticoagulant effect when clarithromycin and oral anticoagulants are used concomitantly. Anticoagulant parameters should be closely monitored. Dose adjustment of the anticoagulant may be necessary. Clarithromycin has also been reported to increase the anticoagulant effect of acenocoumarol.
Triazolobenzodiazepines and other related benzodiazepines	Caution is advised regarding the concomitant administration of clarithromycin with benzodiazepines such as alprazolam, midazolam and triazolam because of the serious risk of CNS effects (e.g., somnolence and confusion).
Calcium Channel Blockers	Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem, nifedipine) because of the risk of hypotension. Hypotension, bradyarrhythmias and lactic acidosis have been observed during concomitant treatment with verapamil. Hypotension and peripheral edema were observed when clarithromycin was taken concomitantly with nifedipine.
Cilostazol	Elevated cilostazol concentrations and increased incidence of headache were observed when clarithromycin was taken concomitantly with cilostazol.
Colchicine	Colchicine is a substrate for both CYP3A and the P-gp transporter. Clarithromycin and other macrolides are known to inhibit CYP3A and P-gp. When clarithromycin and colchicine are used concomitantly, inhibition of P-gp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine.
Digoxin	Serum digoxin levels may be elevated resulting in digoxin toxicity (clinical signs include potentially fatal arrhythmias) in some patients. Monitoring of serum digoxin levels is recommended, particularly in patients with digoxin concentrations in the upper therapeutic range.
Disulfiram	Fatal toxic epidermal necrolysis and fulminant hepatitis have been reported after starting clarithromycin treatment in a patient who was receiving disulfiram.
Ergot alkaloids (Ergotamine, dihydroergotamine)	Acute ergot toxicity characterized by severe peripheral vasospasm, dysesthesia (disorder of any sense, especially of touch), and ischemia of the extremities and other tissues including the CNS has occurred. Cardiac arrhythmias, QT prolongation, ventricular tachycardia, ventricular fibrillation, and *torsades de pointes*) which may lead to death have been reported when the drugs are given concomitantly.
Fluconazole	Concomitant administration resulted in increased steady-state trough serum concentrations and AUC of clarithromycin by 33% and 18%, respectively. Steady-state concentrations of the antimicrobially active metabolite 14-OH clarithromycin were not significantly affected by fluconazole.
Fluoxetine	Delirium has been reported following use of clarithromycin with fluoxetine.
Itraconazole	Concomitant administration may result in increased plasma levels of both clarithromycin and itraconazole. Patients should be monitored closely for signs or symptoms of increased or prolonged adverse reactions.
Omeprazole,