CLARITHROMYCIN EXTENDED RELEASE- clarithromycin tablet, film coated, extended release
Ranbaxy Pharmaceuticals Inc.

Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of clarithromycin extended-release tablets and other antibacterial drugs, clarithromycin extended-release tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6- *O*-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. The structural formula is:

Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water.

Clarithromycin is available as extended-release tablets.

Each yellow oval-shaped film-coated clarithromycin extended-release tablet for oral administration contains 1 gram clarithromycin, USP and the following inactive ingredients: ammonium hydroxide, colloidal silicon dioxide, D&C yellow no. 10 aluminum lake, hydroxypropyl cellulose, hypromellose, iron oxide black, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate, povidone, propylene glycol, shellac, sodium stearyl fumarate, talc, titanium dioxide.

Meets USP Dissolution Test 3.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. For a single 500 mg dose of clarithromycin, food slightly delays the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH clarithromycin or its peak plasma

concentration but does slightly decrease the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, clarithromycin tablets may be given without regard to food.

In nonfasting healthy human subjects (males and females), peak plasma concentrations were attained within 2 to 3 hours after oral dosing. Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 1 to 2 mcg/mL with a 250 mg dose administered every 12 hours and 3 to 4 mcg/mL with a 500 mg dose administered every 8 to 12 hours. The elimination half-life of clarithromycin was about 3 to 4 hours with 250 mg administered every 12 hours but increased to 5 to 7 hours with 500 mg administered every 8 to 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 8 to 12 hours. With a 250 mg every 12 hours dosing, the principal metabolite, 14-OH clarithromycin, attains a peak steady-state concentration of about 0.6 mcg/mL and has an elimination half-life of 5 to 6 hours. With a 500 mg every 8 to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is slightly higher (up to 1 mcg/mL), and its elimination half-life is about 7 to 9 hours. With any of these dosing regimens, the steady-state concentration of this metabolite is generally attained within 3 to 4 days.

After a 250 mg tablet every 12 hours, approximately 20% of the dose is excreted in the urine as clarithromycin, while after a 500 mg tablet every 12 hours, the urinary excretion of clarithromycin is somewhat greater, approximately 30%. In comparison, after an oral dose of 250 mg (125 mg/5 mL) suspension every 12 hours, approximately 40% is excreted in urine as clarithromycin. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10% to 15% of the dose with either a 250 mg or a 500 mg tablet administered every 12 hours.

Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of 500 mg doses of clarithromycin every 12 hours to adult patients with HIV infection were similar to those observed in healthy volunteers. In adult HIV-infected patients taking 500 or 1000 mg doses of clarithromycin every 12 hours, steady-state clarithromycin Cmax values ranged from 2 to 4 mcg/mL and 5 to 10 mcg/mL, respectively.

The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects.

The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function. (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**.)

Clarithromycin and the 14-OH clarithromycin metabolite distribute readily into body tissues and fluids. There are no data available on cerebrospinal fluid penetration. Because of high intracellular concentrations, tissue concentrations are higher than serum concentrations. Examples of tissue and serum concentrations are presented below.

CONCENTRATION (after 250 mg q12h)

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

Clarithromycin extended-release tablets provide extended absorption of clarithromycin from the gastrointestinal tract after oral administration. Relative to an equal total daily dose of immediate-release clarithromycin tablets, clarithromycin extended-release tablets provide lower and later steady-state peak

plasma concentrations but equivalent 24-hour AUC's for both clarithromycin and its microbiologically-active metabolite, 14-OH clarithromycin. While the extent of formation of 14-OH clarithromycin following administration of clarithromycin extended-release tablets (2 x 500 mg once daily) is not affected by food, administration under fasting conditions is associated with approximately 30% lower clarithromycin AUC relative to administration with food. Therefore, clarithromycin extended-release tablets should be taken with food.

In healthy human subjects, steady-state peak plasma clarithromycin concentrations of approximately 2 to 3 mcg/mL were achieved about 5 to 8 hours after oral administration of 2 x 500 mg clarithromycin extended-release tablets once daily; for 14-OH clarithromycin, steady-state peak plasma concentrations of approximately 0.8 mcg/mL were attained about 6 to 9 hours after dosing. Steady-state peak plasma clarithromycin concentrations of approximately 1 to 2 mcg/mL were achieved about 5 to 6 hours after oral administration of a single 500 mg clarithromycin extended-release tablet once daily; for 14-OH clarithromycin, steady-state peak plasma concentrations of approximately 0.6 mcg/mL were attained about 6 hours after dosing.

The following pharmacokinetic data is from Ranbaxy's study of clarithromycin extended-release tablets 1000 mg and clarithromycin extended-release tablets 500 mg. Clarithromycin extended-release tablets 1000 mg produced blood levels similar to those achieved with the two doses of clarithromycin extended-release tablets 500 mg. Orally administered doses of clarithromycin extended-release tablets 1000 mg result in average peak blood levels of clarithromycin in 10.985 hours and for clarithromycin extended-release tablets 500 mg in 9.588 hours after administration in fasting conditions.

Oral administration of single doses of clarithromycin extended-release tablets 1000 mg and two doses of clarithromycin extended-release tablets 500 mg to 34 adult volunteers yielded the following comparable pharmacokinetic data under fasting conditions.

Dose¶	ln AUC_{0-t} (ng.h/mL)	C_{max} (ng/mL)
1000 mg (clarithromycin extended-release)(one tablet)	36645.0248	2188.4419
2 x 500 mg (clarithromycin extended-release)(two tablets)	37615.9151	2206.2014

¶Dosing was following an overnight fast.

Orally administered single doses of clarithromycin extended-release tablets 1000 mg result in average peak blood levels in 6.118 hours and two doses of clarithromycin extended-release tablets 500 mg in 6.235 hours after administration under fed conditions. Oral administration of single doses of clarithromycin extended-release tablets 1000 mg and two doses of clarithromycin extended-release tablets 500 mg to 34 adult volunteers yielded the following comparable pharmacokinetic data under fed

conditions.

Dose*	ln AUC_{0-t} (ng.h/mL)	C_{max} (ng/mL)
1000 mg (clarithromycin extended-release)(one tablet)	58485.5053	3957.2018
2 x 500 mg (clarithromycin extended-release)(two tablets)	60796.1185	3478.3286

* Dosing was following a high fat high calorie breakfast.

For information about other drugs indicated in combination with clarithromycin, refer to the CLINICAL PHARMACOLOGY section of their package inserts.

Microbiology

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of protein synthesis.

Clarithromycin is active in vitro against a variety of aerobic and anaerobic gram-positive and gram-negative microorganisms as well as most Mycobacterium avium complex (MAC) microorganisms.

Additionally, the 14-OH clarithromycin metabolite also has clinically significant antimicrobial activity. The 14-OH clarithromycin is twice as active against Haemophilus influenzae microorganisms as the parent compound. However, for Mycobacterium avium complex (MAC) isolates the 14-OH metabolite is 4 to 7 times less active than clarithromycin. The clinical significance of this activity against Mycobacterium avium complex is unknown.

Clarithromycin has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section:

Aerobic Gram-positive microorganisms

Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic Gram-negative Microorganisms

Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis

Other Microorganisms

Mycoplasma pneumoniae
Chlamydia pneumoniae (TWAR)

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

Aerobic Gram-positive Microorganisms

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

Aerobic Gram-negative Microorganisms

Bordetella pertussis Legionella pneumophila Pasteurella multocida

Anaerobic Gram-positive Microorganisms

Clostridium perfringens Peptococcus niger Propionibacterium acnes

Anaerobic Gram-negative Microorganisms

Prevotella melaninogenica (formerly Bacteriodes melaninogenicus)

Susceptibility Testing:

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method [1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of clarithromycin powder. The MIC values should be interpreted according to the following criteria:

For testing Staphylococcus spp.

MIC (mcg/mL)	**Interpretation**
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

For testing Streptococcus spp. including Streptococcus pneumoniae [a]

MIC (mcg/mL)	**Interpretation**
≤ 0.25	Susceptible (S)
0.5	Intermediate (I)
≥ 1	Resistant (R)

a These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.

For testing Haemophilus spp.[b]

MIC (mcg/mL)	**Interpretation**
≤ 8	Susceptible (S)
16	Intermediate (I)
≥ 32	Resistant (R)

b These interpretive standards are applicable only to broth microdilution susceptibility tests with Haemophilus spp. using Haemophilus Testing Medium (HTM). [1]

Note: When testing *Streptococcus* spp., including *Streptococcus pneumoniae*, susceptibility and resistance to clarithromycin can be predicted using erythromycin.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A

report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin powder should provide the following MIC values:

Microorganism		**MIC (mcg/mL)**
S. aureus	ATCC 29213	0.12 to 0.5
S. pneumoniae[c]	ATCC 49619	0.03 to 0.12
Haemophilus influenzae[d]	ATCC 49247	4 to 16

c This quality control range is applicable only to *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.

d This quality control range is applicable only to *H. influenzae* ATCC 49247 tested by a microdilution procedure using HTM[1].

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure [2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 mcg clarithromycin to test the susceptibility of microorganisms to clarithromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 mcg clarithromycin disk should be interpreted according to the following criteria:

For testing Staphylococcus spp.

Zone diameter (mm)	**Interpretation**
≥ 18	Susceptible (S)
14 to 17	Intermediate (I)
≤ 13	Resistant (R)

For testing Streptococcus spp. including Streptococcus pneumoniae[e]

Zone diameter (mm)	**Interpretation**
≥ 21	Susceptible (S)
17 to 20	Intermediate (I)
≤ 16	Resistant (R)

e These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

For testing Haemophilus spp.[f]

Zone diameter (mm)	**Interpretation**
≥ 13	Susceptible (S)
11 to 12	Intermediate (I)
≤ 10	Resistant (R)

f These zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM[2].

Note: When testing *Streptococcus* spp., including *Streptococcus pneumoniae*, susceptibility and resistance to clarithromycin can be predicted using erythromycin.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves

correlation of the diameter obtained in the disk test with the MIC for clarithromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15 mcg clarithromycin disk should provide the following zone diameters in this laboratory test quality control strain:

Microorganism		**Zone diameter (mm)**
S. aureus	ATCC 25923	26 to 32
S. pneumoniae[g]	ATCC 49619	25 to 31
Haemophilus influenzae[h]	ATCC 49247	11 to 17

g This quality control range is applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.

h This quality control limit applies to tests conducted with *H. influenzae* ATCC 49247 using HTM[2].

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of clarithromycin extended-release tablets and other antibacterial drugs, clarithromycin extended-release tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

THE EFFICACY AND SAFETY OF CLARITHROMYCIN EXTENDED-RELEASE TABLETS IN TREATING OTHER INFECTIONS FOR WHICH OTHER FORMULATIONS OF CLARITHROMYCIN ARE APPROVED HAVE NOT BEEN ESTABLISHED.

CONTRAINDICATIONS

Clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, or any of the macrolide antibiotics.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine (see **Drug Interactions**). There have been postmarketing reports of drug interactions when clarithromycin and/or erythromycin are coadministered with cisapride, pimozide, astemizole, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to the inhibition of metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

For information about contraindications of other drugs indicated in combination with clarithromycin, refer to the **CONTRAINDICATIONS** section of their package inserts.

WARNINGS

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING THIS DRUG, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. CLARITHROMYCIN HAS DEMONSTRATED ADVERSE EFFECTS OF PREGNANCY OUTCOME AND/OR EMBRYO-FETAL DEVELOPMENT IN MONKEYS, RATS, MICE, AND RABBITS AT DOSES THAT PRODUCED PLASMA LEVELS 2 TO 17 TIMES THE SERUM LEVELS ACHIEVED IN HUMANS TREATED AT THE MAXIMUM RECOMMENDED HUMAN DOSES. (See PRECAUTIONS - Pregnancy.)

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 leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. 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.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

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

For information about warnings of other drugs indicated in combination with clarithromycin, refer to the **WARNINGS** section of their package inserts.

PRECAUTIONS

General

Prescribing clarithromycin extended-release tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Clarithromycin is principally excreted via the liver and kidney. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.

Clarithromycin in combination with ranitidine bismuth citrate therapy is not recommended in patients with creatinine clearance less than 25 mL/min. (See **DOSAGE AND ADMINISTRATION**.)

Clarithromycin in combination with ranitidine bismuth citrate should not be used in patients with a history of acute porphyria.

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

For information about precautions of other drugs indicated in combination with clarithromycin, refer to the **PRECAUTIONS** section of their package inserts.

Information to Patients

Patients should be counseled that antibacterial drugs including clarithromycin extended-release tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When clarithromycin extended-release tablet is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by clarithromycin extended-release tablets or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody

stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Clarithromycin may interact with some drugs; therefore patients should be advised to report to their doctor the use of any other medications.

Clarithromycin extended-release tablets should be taken with food.

Drug Interactions

Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range. In two studies in which theophylline was administered with clarithromycin (a theophylline sustained-release formulation was dosed at either 6.5 mg/kg or 12 mg/kg together with 250 or 500 mg q12h clarithromycin), the steady-state levels of C_{max}, C_{min}, and the area under the serum concentration time curve (AUC) of theophylline increased about 20%.

Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered.

When clarithromycin and terfenadine were coadministered, plasma concentrations of the active acid metabolite of terfenadine were threefold higher, on average, than the values observed when terfenadine was administered alone. The pharmacokinetics of clarithromycin and the 14-hydroxy-clarithromycin were not significantly affected by coadministration of terfenadine once clarithromycin reached steady-state conditions. Concomitant administration of clarithromycin with terfenadine is contraindicated. (See **CONTRAINDICATIONS**.)

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients resulted in decreased steady-state zidovudine concentrations. When 500 mg of clarithromycin were administered twice daily, steady-state zidovudine AUC was reduced by a mean of 12% (n = 4). Individual values ranged from a decrease of 34% to an increase of 14%. Based on limited data in 24 patients, when clarithromycin tablets were administered two to four hours prior to oral zidovudine, the steady-state zidovudine Cmax was increased by approximately 2-fold, whereas the AUC was unaffected.

Simultaneous administration of clarithromycin tablets and didanosine to 12 HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.

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 clarithromycin Cmin and AUC of 33% and 18%, respectively. Steady-state concentrations of 14-OH clarithromycin were not significantly affected by concomitant administration of fluconazole.

Concomitant administration of clarithromycin and ritonavir (n = 22) resulted in a 77% increase in clarithromycin AUC and a 100% decrease in the AUC of 14-OH clarithromycin. Clarithromycin may be administered without dosage adjustment to patients with normal renal function taking ritonavir. However, for patients with renal impairment, the following dosage adjustments should be considered. For patients with CL_{CR} 30 to 60 mL/min, the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} < 30 mL/min, the dose of clarithromycin should be decreased by 75%.

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

Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in postmarketing surveillance. Some patients have shown clinical signs

consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Colchicine is a substrate for both CYP3A and the efflux transporter, Pglycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity. (See **WARNINGS**.)

Erythromycin and clarithromycin are substrates and inhibitors of the 3A isoform subfamily of the cytochrome P450 enzyme system (CYP3A). Coadministration of erythromycin or clarithromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. 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 or erythromycin.

The following are examples of some clinically significant CYP3A based drug interactions. Interactions with other drugs metabolized by the CYP3A isoform are also possible. Increased serum concentrations of carbamazepine and the active acid metabolite of terfenadine were observed in clinical trials with clarithromycin.

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

Antiarrhythmics

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

Ergotamine/Dihydroergotamine

Post-marketing reports indicate that coadministration 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 with ergotamine or dihydroergotamine is contraindicated (see **CONTRAINDICATIONS**).

Triazolobenziodidiazepines (Such as Triazolam and Alprazolam) and Related Benzodiazepines (Such as Midazolam)

Erythromycin has been reported to decrease the clearance of triazolam and midazolam, and thus, may increase the pharmacologic effect of these benzodiazepines. There have been post-marketing reports of drug interactions and CNS effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam.

HMG-CoA Reductase Inhibitors

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

Sildenafil (Viagra)

Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. A similar interaction may occur with clarithromycin; reduction of sildenafil dosage should be considered. (See Viagra package insert.)

There have been spontaneous or published reports of CYP3A based interactions of erythromycin and/or clarithromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol, and bromocriptine.

Concomitant administration of clarithromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated (see **CONTRAINDICATIONS**.)

In addition, there have been reports of interactions of erythromycin or clarithromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The following *in vitro* mutagenicity tests have been conducted with clarithromycin:

Salmonella/Mammalian Microsomes Test

Bacterial Induced Mutation Frequency Test

*In Vitro*Chromosome Aberration Test

Rat Hepatocyte DNA Synthesis Assay

Mouse Lymphoma Assay

Mouse Dominant Lethal Study

Mouse Micronucleus Test

All tests had negative results except the *In Vitro* Chromosome Aberration Test which was weakly positive in one test and negative in another.

In addition, a Bacterial Reverse-Mutation Test (Ames Test) has been performed on clarithromycin metabolites with negative results.

Fertility and reproduction studies have shown that daily doses of up to 160 mg/kg/day (1.3 times the recommended maximum human dose based on mg/m^2) to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after 150 mg/kg/day were 2 times the human serum levels.

In the 150 mg/kg/day monkey studies, plasma levels were 3 times the human serum levels. When given orally at 150 mg/kg/day (2.4 times the recommended maximum human dose based on mg/m^2), clarithromycin was shown to produce embryonic loss in monkeys. This effect has been attributed to marked maternal toxicity of the drug at this high dose.

In rabbits, *in utero* fetal loss occurred at an intravenous dose of 33 mg/m^2, which is 17 times less than the maximum proposed human oral daily dose of 618 mg/m^2.

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of clarithromycin.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Four teratogenicity studies in rats (three with oral doses and one with intravenous doses up to 160 mg/kg/day administered during the period of major organogenesis) and two in rabbits at oral doses up to 125 mg/kg/day (approximately 2 times the recommended maximum human dose based on mg/m^2) or intravenous doses of 30 mg/kg/day administered during gestation days 6 to 18 failed to demonstrate any teratogenicity from clarithromycin. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6 to 15. Plasma levels after 150 mg/kg/day were 2 times

the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day (2 and 4 times the recommended maximum human dose based on mg/m^2, respectively) during gestation days 6 to 15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day exposure resulted in plasma levels 17 times the human serum levels. In monkeys, an oral dose of 70 mg/kg/day (an approximate equidose of the recommended maximum human dose based on mg/m^2) produced fetal growth retardation at plasma levels that were 2 times the human serum levels.

There are no adequate and well-controlled studies in pregnant women. Clarithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

Nursing Mothers

It is not known whether clarithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when clarithromycin is administered to a nursing woman. It is known that clarithromycin is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk. Preweaned rats, exposed indirectly via consumption of milk from dams treated with 150 mg/kg/day for 3 weeks, were not adversely affected, despite data indicating higher drug levels in milk than in plasma.

Pediatric Use

Safety and effectiveness of clarithromycin in pediatric patients under 6 months of age have not been established. The safety of clarithromycin has not been studied in MAC patients under the age of 20 months. Neonatal and juvenile animals tolerated clarithromycin in a manner similar to adult animals. Young animals were slightly more intolerant to acute overdosage and to subtle reductions in erythrocytes, platelets and leukocytes but were less sensitive to toxicity in the liver, kidney, thymus, and genitalia.

Geriatric Use

In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 500 mg every 12 hours, the maximum serum concentrations and area under the curves of clarithromycin and 14-OH clarithromycin were increased compared to those achieved in healthy young adults. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients. Dosage adjustment should be considered in elderly patients with severe renal impairment.

ADVERSE REACTIONS

The majority of side effects observed in clinical trials were of a mild and transient nature. Fewer than 3% of adult patients without mycobacterial infections and fewer than 2% of pediatric patients without mycobacterial infections discontinued therapy because of drug-related side effects. Fewer than 2% of adult patients taking clarithromycin extended-release tablets discontinued therapy because of drug-related side effects

The most frequently reported events in adults taking clarithromycin extended-release tablets, were diarrhea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). In pediatric patients, the most frequently reported events were diarrhea (6%), vomiting (6%), abdominal pain (3%), rash (3%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% was described as severe.

The most frequently reported events in adults taking clarithromycin extended-release tablets were diarrhea (6%), abnormal taste (7%), and nausea (3%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, less than 1% were described as severe.

In the acute exacerbation of chronic bronchitis and acute maxillary sinusitis studies overall gastrointestinal adverse events were reported by a similar proportion of patients taking either

clarithromycin tablets or clarithromycin extended-release tablets; however, patients taking clarithromycin extended-release tablets reported significantly less severe gastrointestinal symptoms compared to patients taking clarithromycin tablets. In addition, patients taking clarithromycin extended-release tablets had significantly fewer premature discontinuations for drug-related gastrointestinal or abnormal taste adverse events compared to clarithromycin tablets.

In community-acquired pneumonia studies conducted in adults comparing clarithromycin to erythromycin base or erythromycin stearate, there were fewer adverse events involving the digestive system in clarithromycin-treated patients compared to erythromycin-treated patients (13% vs 32%; $p < 0.01$). Twenty percent of erythromycin-treated patients discontinued therapy due to adverse events compared to 4% of clarithromycin-treated patients.

In two U.S. studies of acute otitis media comparing clarithromycin to amoxicillin/potassium clavulanate in pediatric patients, there were fewer adverse events involving the digestive system in clarithromycin-treated patients compared to amoxicillin/potassium clavulanate-treated patients (21% vs. 40%, $p < 0.001$). One-third as many clarithromycin-treated patients reported diarrhea as did amoxicillin/potassium clavulanate-treated patients.

Post-Marketing Experience

Allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred. Other spontaneously reported adverse events include glossitis, stomatitis, oral moniliasis, anorexia, vomiting, pancreatitis, tongue discoloration, thrombocytopenia, leukopenia, neutropenia, and dizziness. There have been reports of tooth discoloration in patients treated with clarithromycin. Tooth discoloration is usually reversible with professional dental cleaning. There have been isolated reports of hearing loss, which is usually reversible, occurring chiefly in elderly women. Reports of alterations of the sense of smell, usually in conjunction with taste perversion or taste loss have also been reported.

Transient CNS events including anxiety, behavioral changes, confusional states, convulsions, depersonalization, disorientation, hallucinations, insomnia, manic behavior, nightmares, psychosis, tinnitus, tremor, and vertigo have been reported during post-marketing surveillance. Events usually resolve with discontinuation of the drug.

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.

There have been rare reports of hypoglycemia, some of which have occurred in patients taking oral hypoglycemic agents or insulin.

There have been postmarketing reports of clarithromycin extended-release 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.

As with other macrolides, clarithromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes.

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

Changes in Laboratory Values

Changes in laboratory values with possible clinical significance were as follows:

Hepatic

elevated SGPT (ALT) < 1%; SGOT (AST) < 1%; GGT < 1%; alkaline phosphatase < 1%; LDH < 1%;

total bilirubin < 1%

Hematologic

decreased WBC < 1%; elevated prothrombin time 1%

Renal

elevated BUN 4%; elevated serum creatinine < 1%

GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.

OVERDOSAGE

Overdosage of clarithromycin can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea.

Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum concentrations are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

Clarithromycin extended-release tablets should be taken with food.

Clarithromycin extended-release tablets should be swallowed whole and not chewed, broken or crushed.

ADULT DOSAGE GUIDELINES

	Clarithromycin Extended-Release Tablets	
Infection	**Dosage** (q24h)	**Duration** (days)
Acute maxillary sinusitis due to	1 gram	14
H. influenzae		
M. catarrhalis		
S. pneumoniae		
Acute exacerbation of chronic bronchitis due to		
H. influenzae	1 gram	7
H. parainfluenzae	1 gram	7
M. catarrhalis	1 gram	7
S. pneumoniae	1 gram	7
Community-Acquired Pneumonia due to		
H. influenzae	1 gram	7
H. parainfluenzae	1 gram	7
M. catarrhalis	1 gram	7
S. pneumoniae	1 gram	7
C. pneumoniae	1 gram	7
M. pneumoniae	1 gram	7

HOW SUPPLIED

Clarithromycin extended-release tablets, 1000 mg are yellow-colored, oval-shaped, film coated tablets

imprinted with ‘RB 36’ in black ink on one side and plain on the other side. They are supplied as follows:

NDC 63304-971-03 Bottles of 10

NDC 63304-971-54 Blister unit-dose of 14

NDC 63304-971-05 Bottles of 500

NDC 63304-971-70 Blister unit-dose of 70

Store at 20 - 25° C (68 - 77° F) (See USP Controlled Room Temperature)

REFERENCES

1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. NCCLS, Wayne, PA, January 1997.
2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January, 1997.
3. National Committee for Clinical Laboratory Standards. Summary Minutes, Subcommittee on Antimicrobial Susceptibility Testing, Tampa, FL. January 11-13, 1998.

Manufactured for:

Ranbaxy Pharmaceuticals Inc.

Jacksonville, FL 32257 USA

by: Ranbaxy Laboratories Limited

New Delhi – 110 019, India

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CLARITHROMYCIN EXTENDED RELEASE

clarithromycin tablet, film coated, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:66304-971
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Clarithromycin (UNII: H1250JIK0A) (Clarithromycin - UNII:H1250JIK0A)		1000 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ammonium hydroxide ()	
colloidal silicon dioxide (UNII: ETJ7Z6XBU4)	
D & C yellow No 10 aluminum lake ()	

hydroxypropyl cellulose (UNII: RFW2ET671P)	
hypromellose ()	
iron oxide black (UNII: XM0M87F357)	
lactose monohydrate (UNII: EWQ57Q8I5X)	
magnesium stearate (UNII: 70097M6I30)	
polyethylene glycol ()	
polysorbate ()	
povidone (UNII: FZ989GH94E)	
propylene glycol (UNII: 6DC9Q167V3)	
shellac ()	
sodium stearyl ()	
fumarate ()	
talc (UNII: 7SEV7J4R1U)	
titanium dioxide (UNII: 15FIX9V2JP)	

Product Characteristics

Color	yellow	**Score**	no score
Shape	OVAL	**Size**	8mm
Flavor		**Imprint Code**	RB;36
Contains			
Coating	true	**Symbol**	false

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66304-971-10	10 in 1 BOTTLE		
2	NDC:63304-971-05	500 in 1 BOTTLE		
3	NDC:63304-971-14	14 in 1 BOX, UNIT-DOSE		
4	NDC:63304-971-70	70 in 1 BOX, UNIT-DOSE		

Labeler - Ranbaxy Pharmaceuticals Inc.

Revised: 8/2008 Ranbaxy Pharmaceuticals Inc.