

CLARITHROMYCIN- clarithromycin tablet, film coated, extended release
RedPharm Drug, Inc.

SPL UNCLASSIFIED SECTION

Rx Only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of clarithromycin extended-release tablets and other antibacterial drugs, clarithromycin 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 C₃₈H₆₉NO₁₃, and the molecular weight is 747.96. The structural formula is:

[Clarithromycin structural formula]

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.

Each yellow oval film-coated clarithromycin extended-release tablet, for oral administration, contains 500 mg of clarithromycin and the following inactive ingredients: compressible sugar, D&C yellow #10 Lake, glycerol monostearate, polyethylene glycol 3000, polyvinyl alcohol, sodium phosphate monobasic (anhydrous), talc and titanium dioxide.

Meets USP requirements for dissolution test 2.

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 C_{max} 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 × 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.

[Steady-State Clarithromycin Plasma Concentration-Time Profiles]

Steady-State Clarithromycin Plasma Concentration-Time Profiles

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.

Microbiology

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

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

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:

Gram-Positive Microorganisms

Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes

Gram-Negative Microorganisms

Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis

Other Microorganisms

Mycoplasma pneumoniae

Chlamydomphila pneumoniae (TWAR) [previously *Chlamydia pneumoniae*]

The following in vitro data are available, but their clinical significance is unknown.

Clarithromycin exhibits in vitro activity against most isolates of the following bacteria; however, the safety and effectiveness of clarithromycin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Gram-Positive Bacteria

Streptococcus agalactiae

Streptococci (Groups C, F, G)

Viridans group streptococci

Gram-Negative Bacteria

Bordetella pertussis

Legionella pneumophila

Pasteurella multocida

Gram-Positive Bacteria

Clostridium perfringens

Peptococcus niger

Propionibacterium acnes

Gram-Negative Anaerobic Bacteria

Prevotella melaninogenica (formerly *Bacteriodes melaninogenicus*)

Susceptibility Testing Methods

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 method¹ (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 criteria²:

Susceptibility Test Interpretive Criteria for *Staphylococcus aureus*

MIC (mcg/mL) Interpretation

≤ 2.0 Susceptible (S)

4.0 Intermediate (I)

≥ 8.0 Resistant (R)

Susceptibility Test Interpretive Criteria for *Streptococcus pyogenes* and *Streptococcus pneumoniae*

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

MIC (mcg/mL) Interpretation

≤ 0.25 Susceptible (S)

0.5 Intermediate (I)

≥ 1.0 Resistant (R)

For testing *Haemophilus* spp. b

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 pyogenes* and *Streptococcus pneumoniae*, susceptibility and resistance to clarithromycin can be predicted using erythromycin.

MIC (mcg/mL) Interpretation

≤ 8.0 Susceptible (S)

16.0 Intermediate (I)

≥ 32.0 Resistant (R)

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.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control bacteria to monitor and ensure the accuracy and precision of supplies and reagents in the assay, and the techniques of the individual performing the test.^{1,2} Standard clarithromycin powder should provide the following MIC ranges.

cATCC is a registered trademark of the American Type Culture Collection.

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

e This quality control range is applicable only to *H. influenzae* ATCC 49247 tested by a microdilution procedure using HTM1.

QC Strain MIC (mcg/mL)

S. aureus ATCC® 29213c 0.12 to 0.5

S. pneumoniae ATCC 49619 0.03 to 0.12

Haemophilus influenzae ATCC 49247 4 to 16

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized method.^{2,3} The procedure uses paper disks impregnated with 15 mcg of clarithromycin to test the susceptibility of bacteria. The disk diffusion interpretive criteria are provided below.

Susceptibility Test Interpretive Criteria for *Staphylococcus aureus*

Zone diameter (mm) Interpretation

≥ 18 Susceptible (S)

14 to 17 Intermediate (I)

≤ 13 Resistant (R)

Susceptibility Test Interpretive Criteria for *Streptococcus pyogenes* and *Streptococcus pneumoniae* f

f These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO₂.

Zone diameter (mm) Interpretation

≥ 21 Susceptible (S)

17 to 20 Intermediate (I)

≤ 16 Resistant (R)

For testing *Haemophilus* spp. g

g These zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM2.

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

Zone diameter (mm) Interpretation

≥ 13 Susceptible (S)

11 to 12 Intermediate (I)

≤ 10 Resistant (R)

Quality Control

Standardized susceptibility test procedures require the use of laboratory control bacteria to monitor and ensure the accuracy and precision of supplies and reagents in the assay, and the techniques of the individual performing the test.^{2,3} For the diffusion technique using the 15 mcg disk, the criteria in the following table should be achieved.

Acceptable Quality Control Ranges for Clarithromycin

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

i This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using HTM2.

INDICATIONS AND USAGE

Adults (Clarithromycin Extended-Release Tablets, USP)

Clarithromycin extended-release tablets, USP are indicated for the treatment of adults with mild to moderate infection caused by susceptible strains of the designated microorganisms in the conditions listed below:

Acute maxillary sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.

Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.

Community-Acquired Pneumonia due to *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Chlamydophila pneumoniae* (TWAR), or *Mycoplasma pneumoniae*.

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of clarithromycin extended-release tablets, USP and other antibacterial drugs, clarithromycin extended-release tablets, USP 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.

CONTRAINDICATIONS

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

Clarithromycin is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of clarithromycin.

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 inhibition of metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

Concomitant administration of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment.

Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointes.

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. (see WARNINGS).

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

WARNINGS

Use In Pregnancy

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).

Hepatotoxicity

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Symptoms of hepatitis can include anorexia, jaundice, dark urine, pruritus, or tender abdomen. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur.

QT Prolongation

Clarithromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving clarithromycin. Fatalities have been reported. Clarithromycin should be avoided in patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia (see CONTRAINDICATIONS) and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Drug Interactions

Serious adverse reactions have been reported in patients taking clarithromycin concomitantly with CYP3A4 substrates. These include colchicine toxicity with colchicine; rhabdomyolysis with simvastatin, lovastatin, and atorvastatin; hypoglycemia with disopyramide; and hypotension and acute kidney injury with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem, nifedipine). Most reports of acute kidney injury with calcium channel blockers metabolized by CYP3A4 involved elderly patients 65 years of age or older (see CONTRAINDICATIONS and PRECAUTIONS - DRUG INTERACTIONS). Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see PRECAUTIONS - DRUG INTERACTIONS).

Colchicine

Life-threatening and fatal drug interactions have been reported in patients treated with clarithromycin and colchicine. Clarithromycin is a strong CYP3A4 inhibitor and this interaction may occur while using both drugs at their recommended doses. If coadministration of clarithromycin and colchicine is necessary in patients with normal renal and hepatic function, the dose of colchicine should be reduced. Patients should be monitored for clinical symptoms of colchicine toxicity. Concomitant administration of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment (see CONTRAINDICATIONS and PRECAUTIONS - DRUG INTERACTIONS).

Benzodiazepines

Increased sedation and prolongation of sedation have been reported with concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and midazolam.

Quetiapine

Use quetiapine and clarithromycin concomitantly with caution. Coadministration could result in increased quetiapine exposure and quetiapine related toxicities such as somnolence, orthostatic hypotension, altered state of consciousness, neuroleptic

malignant syndrome, and QT prolongation. Refer to quetiapine prescribing information for recommendations on dose reduction if coadministered with CYP3A4 inhibitors such as clarithromycin.

Oral Hypoglycemic Agents/Insulin

The concomitant use of clarithromycin and oral hypoglycemic agents and/or insulin can result in significant hypoglycemia. With certain hypoglycemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycemia when used concomitantly. Careful monitoring of glucose is recommended.

Oral Anticoagulants

There is a risk of serious hemorrhage and significant elevations in INR and prothrombin time when clarithromycin is coadministered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

HMG-CoA Reductase Inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see CONTRAINDICATIONS) 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. Cases of rhabdomyolysis have been reported in 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 atorvastatin or pravastatin cannot be avoided, atorvastatin dose should not exceed 20 mg daily and pravastatin dose should not exceed 40 mg daily. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered. It is recommended to prescribe the lowest registered dose if concomitant use cannot be avoided.

Clostridium difficile Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including clarithromycin extended-release tablets, 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.

Acute Hypersensitivity Reactions

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), and Henoch-Schonlein purpura clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Combination Therapy with Other Drugs

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.

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

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 tablets are 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%.

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class.

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-OH-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 may result in decreased steady-state zidovudine concentrations. Following administration of clarithromycin 500 mg tablets twice daily with zidovudine 100 mg every 4 hours, the steady-state zidovudine AUC decreased 12% compared to administration of zidovudine alone (n=4). Individual values ranged from a decrease of 34% to an increase of 14%. When clarithromycin tablets were administered two to four hours prior to zidovudine, the steady-state zidovudine C_{max} increased 100% whereas the AUC was unaffected (n=24). Administration of clarithromycin and zidovudine should be separated by at least two hours. The impact of coadministration of clarithromycin extended-release tablets and zidovudine has not been evaluated.

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

Following administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers, the steady-state clarithromycin C_{min} and AUC increased 33% and 18%, respectively. Steady-state concentrations of 14-OH clarithromycin were not significantly affected by concomitant administration of fluconazole. No dosage adjustment of clarithromycin is necessary when coadministered with fluconazole.

Ritonavir

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. Since concentrations of 14-OH clarithromycin are significantly reduced when clarithromycin is coadministered with ritonavir, alternative antibacterial therapy should be considered for indications other than infections due to *Mycobacterium avium* complex (see PRECAUTIONS - DRUG INTERACTIONS). Doses of clarithromycin greater than 1000 mg per day should not be coadministered with protease inhibitors.

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.

Digoxin is a substrate for P-glycoprotein (Pgp) and clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are coadministered, inhibition of Pgp by clarithromycin may lead to increased exposure of digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have been reported in postmarketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Monitoring of serum digoxin concentrations should be considered, especially for patients with digoxin concentrations in the upper therapeutic range.

Coadministration 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 are examples of some clinically significant CYP3A based drug interactions. Interactions with other drugs metabolized by the CYP3A isoform are also possible.

Carbamazepine and Terfenadine

Increased serum concentrations of carbamazepine and the active acid metabolite of terfenadine were observed in clinical trials with clarithromycin.

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 a single dose of colchicine 0.6 mg was administered with clarithromycin 250 mg BID for 7 days, the colchicine C_{max} increased 197% and the AUC_{0-∞} increased 239% compared to administration of colchicine alone. The dose of colchicine should be reduced when coadministered with clarithromycin in patients with normal renal and hepatic function. Concomitant use of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment (see WARNINGS).

Efavirenz, Nevirapine, Rifampicin, Rifabutin, and Rifapentine

Inducers of CYP3A enzymes, such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine will increase the metabolism of clarithromycin, thus decreasing plasma concentrations of clarithromycin, while increasing those of 14-OH-clarithromycin. 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. Alternative antibacterial treatment should be considered when treating patients receiving inducers of CYP3A. 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.

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.

Sildenafil, Tadalafil, and Vardenafil

Each of these phosphodiesterase inhibitors is primarily metabolized by CYP3A, and CYP3A will be inhibited by concomitant administration of clarithromycin. Coadministration of clarithromycin with sildenafil, tadalafil, or vardenafil will result in increased exposure of these phosphodiesterase inhibitors. Coadministration of these phosphodiesterase inhibitors with clarithromycin is not recommended.

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, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. Tolterodine 1 mg twice daily is recommended in patients deficient in CYP2D6 activity (poor metabolizers) when coadministered with clarithromycin.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam)

When a single dose of midazolam was coadministered with clarithromycin tablets (500 mg twice daily for 7 days), midazolam AUC increased 174% after intravenous administration of midazolam and 600% after oral administration. When oral midazolam is coadministered with clarithromycin, dose adjustments may be necessary and possible prolongation and intensity of effect should be anticipated. Caution and appropriate dose adjustments should be considered when triazolam or alprazolam is coadministered with clarithromycin. For benzodiazepines which are not metabolized by CYP3A (e.g., temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

There have been postmarketing 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.

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Following administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily), the clarithromycin AUC increased 94%, the 14-OH clarithromycin AUC decreased 70% and the atazanavir AUC increased 28%. When clarithromycin is coadministered with atazanavir, the dose of clarithromycin should be decreased by 50%. Since concentrations of 14-OH clarithromycin are significantly reduced when clarithromycin is coadministered with atazanavir, alternative antibacterial therapy should be considered for indications other

than infections due to *Mycobacterium avium* complex (see PRECAUTIONS – DRUG INTERACTIONS). Doses of clarithromycin greater than 1000 mg per day should not be coadministered with protease inhibitors.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, potentially leading to a bi-directional drug interaction when administered concomitantly. Clarithromycin may increase the plasma concentrations of itraconazole, while itraconazole may increase the plasma concentrations of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged adverse reactions.

Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A and there is evidence of a bi-directional drug interaction. Following administration of clarithromycin (500 mg bid) and saquinavir (soft gelatin capsules, 1200 mg tid) to 12 healthy volunteers, the steady-state saquinavir AUC and C_{max} increased 177% and 187% respectively compared to administration of saquinavir alone. Clarithromycin AUC and C_{max} increased 45% and 39% respectively, whereas the 14-OH clarithromycin AUC and C_{max} decreased 24% and 34% respectively, compared to administration with clarithromycin alone. No dose adjustment of clarithromycin is necessary when clarithromycin is coadministered with saquinavir in patients with normal renal function. When saquinavir is coadministered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (refer to interaction between clarithromycin and ritonavir) (see PRECAUTIONS – DRUG INTERACTIONS).

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.

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.

Ergotamine/Dihydroergotamine

Postmarketing 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).

Triazolobenzodiazepines (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 postmarketing reports of drug interactions and CNS effects (e.g., somnolence and

confusion) with the concomitant use of clarithromycin and triazolam.

Quetiapine

Quetiapine is a substrate for CYP3A4, which is inhibited by clarithromycin. Coadministration with clarithromycin could result in increased quetiapine exposure and possible quetiapine related toxicities. There have been post-marketing reports of somnolence, orthostatic hypotension, altered state of consciousness, neuroleptic malignant syndrome, and QT prolongation during concomitant administration. Refer to quetiapine prescribing information for recommendations on dose reduction if coadministered with CYP3A4 inhibitors such as clarithromycin.

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, bromocriptine, vinblastine, phenobarbital and St. John's Wort.

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/m²) 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/m²), 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/m², which is 17 times less than the maximum proposed human oral daily dose of 618 mg/m².

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/m²) 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/m², 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/m²) 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

Clarithromycin and its active metabolite 14-hydroxy clarithromycin are excreted in human milk. Serum and milk samples were obtained after 3 days of treatment, at steady state, from one published study of 12 lactating women who were taking clarithromycin 250 mg orally twice daily. Based on the limited data from this study, and assuming milk consumption of 150 mL/kg/day, an exclusively human milk fed infant would receive an estimated average of 136 mcg/kg/day of clarithromycin and its active metabolite, with this maternal dosage regimen. This is less than 2% of the maternal weight-adjusted dose (7.8 mg/kg/day, based on the average maternal weight of 64 kg), and less than 1% of the pediatric dose (15 mg/kg/day) for children greater than 6 months of age.

A prospective observational study of 55 breastfed infants of mothers taking a macrolide antibiotic (6 were exposed to clarithromycin) were compared to 36 breastfed infants of mothers

taking amoxicillin. Adverse reactions were comparable in both groups. Adverse reactions

occurred in 12.7% of infants exposed to macrolides and included rash, diarrhea, loss of appetite, and somnolence.

Caution should be exercised when clarithromycin is administered to nursing women. The development and health benefits of human milk feeding should be considered along with the mother's clinical need for clarithromycin and any potential adverse effects on the human milk fed child from the drug or from the underlying maternal condition.

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. Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients (see WARNINGS and PRECAUTIONS).

Most reports of acute kidney injury with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem, nifedipine) involved elderly patients 65 years of age or older (see WARNINGS).

ADVERSE REACTIONS

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and pediatric populations are abdominal pain, diarrhea, nausea, vomiting and dysgeusia. These adverse reactions 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.

Adverse Reactions Observed During Clinical Trials of Clarithromycin

The following adverse reactions were observed in clinical trials with clarithromycin at a rate greater than or equal to 1%:

Gastrointestinal Disorders

Diarrhea, vomiting, dyspepsia, nausea, abdominal pain

Hepatobiliary Disorders

Liver function test abnormal

Immune System Disorders

Anaphylactoid reaction

Infection and Infestations

Candidiasis

Nervous System Disorders

Dysgeusia, headache

Psychiatric Disorders

Insomnia

Skin and Subcutaneous Tissue Disorders

Rash

Other Adverse Reactions Observed During Clinical Trials of Clarithromycin

The following adverse reactions were observed in clinical trials with clarithromycin at a rate less than 1%:

Blood and Lymphatic System Disorders

Leukopenia, neutropenia, thrombocythemia, eosinophilia

Cardiac Disorders

Electrocardiogram QT prolonged, cardiac arrest, atrial fibrillation, extrasystoles, palpitations

Ear and Labyrinth Disorders

Vertigo, tinnitus, hearing impaired

Gastrointestinal Disorders

Stomatitis, glossitis, esophagitis, gastroesophageal reflux disease, gastritis, proctalgia, abdominal distension, constipation, dry mouth, eructation, flatulence

General Disorders and Administration Site Conditions

Malaise, pyrexia, asthenia, chest pain, chills, fatigue

Hepatobiliary Disorders

Cholestasis, hepatitis

Immune System Disorders

Hypersensitivity

Infections and Infestations

Cellulitis, gastroenteritis, infection, vaginal infection

Investigations

Blood bilirubin increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, albumin globulin ratio abnormal

Metabolism and Nutrition Disorders

Anorexia, decreased appetite

Musculoskeletal and Connective Tissue Disorders

Myalgia, muscle spasms, nuchal rigidity

Nervous System Disorders

Dizziness, tremor, loss of consciousness, dyskinesia, somnolence

Psychiatric Disorders
Anxiety, nervousness

Renal and Urinary Disorders
Blood creatinine increased, blood urea increased

Respiratory, Thoracic and Mediastinal Disorders
Asthma, epistaxis, pulmonary embolism

Skin and Subcutaneous Tissue Disorders
Urticaria, dermatitis bullous, pruritus, hyperhidrosis, rash maculo-papular

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.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of clarithromycin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders
Thrombocytopenia, agranulocytosis

Cardiac Disorders
Torsades de pointes, ventricular tachycardia, ventricular arrhythmia

Ear and Labyrinth Disorders
Deafness was reported chiefly in elderly women and was usually reversible.

Gastrointestinal Disorders
Pancreatitis acute, tongue discoloration, tooth discoloration was reported and was usually reversible with professional cleaning upon discontinuation of the drug. There have been 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. 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 antibacterial drug.

Hepatobiliary Disorders

Hepatic failure, jaundice hepatocellular. Adverse reactions related to hepatic dysfunction have been reported with clarithromycin (see WARNINGS - HEPATOTOXICITY).

Immune System Disorders

Anaphylactic reaction, angioedema

Infections and Infestations

Pseudomembranous colitis

Investigations

Prothrombin time prolonged, white blood cell count decreased, international normalized ratio increased. Abnormal urine color has been reported, associated with hepatic failure.

Metabolism and Nutrition Disorders

Hypoglycemia has been reported in patients taking oral hypoglycemic agents or insulin.

Musculoskeletal and Connective Tissue Disorders

Myopathy, rhabdomyolysis was reported and in some of the reports, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol (see CONTRAINDICATIONS and WARNINGS).

Nervous System Disorders

Convulsion, ageusia, parosmia, anosmia, paraesthesia

Psychiatric Disorders

Psychotic disorder, confusional state, depersonalization, depression, disorientation, manic behavior, hallucination, abnormal behavior, abnormal dreams. These disorders usually resolve upon discontinuation of the drug.

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.

Renal and Urinary Disorders

Nephritis interstitial, renal failure

Skin and Subcutaneous Tissue Disorders

Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), Henoch-Schonlein purpura, acne

Vascular Disorders

Hemorrhage

There have been 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 WARNINGS and PRECAUTIONS).

To report SUSPECTED ADVERSE EVENTS, contact Actavis at 1-800-272-5525 or FDA at 1-800-FDA-1088 or [HTTP://WWW.FDA.GOV/](http://www.fda.gov/) for voluntary reporting of adverse

reactions.

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.

Clarithromycin may be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function. In patients with severe renal impairment (CLCR less than 30 mL/min), the dose of clarithromycin should be reduced by 50%. However, when patients with moderate or severe renal impairment are taking clarithromycin concomitantly with atazanavir or ritonavir, the dose of clarithromycin should be reduced by 50% or 75% for patients with CLCR of 30 to 60 mL/min or less than 30 mL/min, respectively.

ADULT DOSAGE GUIDELINES

Clarithromycin Extended-Release Tablets

Infection Dosage

(q24h) Duration

(days)

Acute maxillary sinusitis due to 2 x 500 mg 14

H.influenzae

M.catarrhalis

S. pneumoniae

Acute exacerbation of chronic bronchitis due to

H.influenzae 2 x 500 mg 7

H. parainfluenzae 2 x 500 mg 7

M. catarrhalis 2 x 500 mg 7

S. pneumoniae 2 x 500 mg 7

Community-Acquired Pneumonia due to

H.influenzae 2 x 500 mg 7

H.parainfluenzae 2 x 500 mg 7

M.catarrhalis 2 x 500 mg 7

S. pneumoniae 2 x 500 mg 7

C.pneumoniae 2 x 500 mg 7

M.pneumoniae 2 x 500 mg 7

HOW SUPPLIED

Clarithromycin extended-release tablets, USP are supplied as yellow, film coated, oval shaped tablets debossed with [Company Logo] and "777" on one side.

Bottles of 60 (NDC 0591-2805-60), bottles of 500 (NDC 0591-2805-05), bottles of 1000 (NDC 0591-2805-10).

Store clarithromycin extended-release tablets, USP at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

ANIMAL PHARMACOLOGY AND TOXICOLOGY

REFERENCES

Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - 9th edition. Approved Standard. CLSI Document M07-A9, CLSI. 950 West Valley Rd, Suite 2500, Wayne, PA 19087, 2012.

CLSI. Performance Standards for Antimicrobial Susceptibility Testing, 23rd Informational Supplement, CLSI Document M100-S23, 2013.

CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests, 11th edition. Approved Standard CLSI Document M02-A11, 2012.

Manufactured by:
Actavis Laboratories FL, Inc.
Fort Lauderdale, FL 33314 USA

Distributed by:
Actavis Pharma, Inc.
Parsippany, NJ 07054 USA

Revised: January 2016

PRINCIPAL DISPLAY PANEL

NDC: 67296-1072-1
CLARITHROMYCIN EXT. REL.
500MG
14 Tablets

Rx Only

Lot: 47405A 1

Exp: 09/15

Usual adult dosage: See package insert
Store at controlled room temperature: 20-25 C (68-77 F)

Mfg. by: Watson Laboratories, Inc
Corona, CA 92880
0591-2805-60

Dist. by: Redpharm Drug Eden Prairie, MN 55344



0
10721
67296
3

LCN: 565460

CLARITHROMYCIN

clarithromycin tablet, film coated, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:67296-1072(NDC:0591-2805)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CLARITHROMYCIN (UNII: H1250JIK0A) (CLARITHROMYCIN - UNII:H1250JIK0A)	CLARITHROMYCIN	500 mg

Inactive Ingredients

Ingredient Name	Strength
SUCROSE (UNII: C151H8M554)	
GLYCERYL MONOSTEARATE (UNII: 230OU9XXE4)	
SODIUM PHOSPHATE, MONOBASIC, ANHYDROUS (UNII: KH7I04HPUU)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
POLYETHYLENE GLYCOL 3000 (UNII: SA1B764746)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	yellow	Score	no score
Shape	OVAL	Size	19mm
Flavor		Imprint Code	777
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67296-1072-1	14 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2008	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA065145	01/01/2008	

Labeler - RedPharm Drug, Inc. (828374897)

Establishment

Name	Address	ID/FEI	Business Operations
RedPharm Drug, Inc.		828374897	repack(67296-1072)

Revised: 1/2022

RedPharm Drug, Inc.