CLARITHROMYCIN abbreviated: clarithromycin tablet, film coated, extended release
PD-Rx Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CLARITHROMYCIN EXTENDED-RELEASE TABLETS safely and effectively. See full prescribing information for CLARITHROMYCIN EXTENDED-RELEASE TABLETS.

CLARITHROMYCIN extended-release tablets, for oral use


INDICATIONS AND USAGE
Clarithromycin is a macrolide antimicrobial indicated for mild to moderate infections caused by designated, susceptible bacteria in the following:
- Acute Bacterial Exacerbation of Chronic Bronchitis in Adults (1.1)
- Acute Maxillary Sinusitis (1.2)
- Community-Acquired Pneumonia (1.3)

Limitations of Use
Clarithromycin extended-release tablets are indicated only for acute bacterial exacerbation of chronic bronchitis, acute maxillary sinusitis, and community-acquired pneumonia in adults. (1.9)
To reduce the development of drug-resistant bacteria and maintain the effectiveness of clarithromycin and other antibacterial drugs, clarithromycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.9)

DOSAGE AND ADMINISTRATION
- Adults: Clarithromycin extended-release tablets 1 gram every 24 hours for 7 to 14 days (2.2)
- Reduce dose in moderate renal impairment with concomitant atazanavir or ritonavir-containing regimens and in severe renal impairment (2.6)

DOSAGE FORMS AND STRENGTHS
- Extended-release Tablets: 500 mg (3)

CONTRAINDICATIONS
- Hypersensitivity to clarithromycin or any macrolide drug (4.1)
- Cisapride, pimozide, lovastatin/simvastatin, ergotamine/dihydroergotamine (4.2, 4.5, 4.6)
- History of cholestatic jaundice/hepatic dysfunction with use of clarithromycin (4.3)
- Colchicine in renal or hepatic impairment (4.4)

WARNINGS AND PRECAUTIONS
- Severe acute hypersensitivity reactions: Discontinue clarithromycin if occurs (5.1)
- QT prolongation: Avoid clarithromycin in patients with known QT prolongation or receiving drugs known to prolong the QT interval, ventricular arrhythmia (torsade de pointes), hypokalemia/hypomagnesemia, significant bradycardia, or taking Class IA or III antiarrhythmics (5.2)
- Hepatotoxicity: Discontinue if signs and symptoms of hepatitis occur (5.3)
- Serious adverse reactions can occur due to drug interactions of clarithromycin with colchicine, some HMG CoA reductase inhibitors, some calcium channel blockers, and other drugs (5.4)
- Risk of all-cause mortality one year or more after the end of treatment in patients with coronary artery disease (5.5)
- Clostridium difficile associated diarrhea (CDAD): Evaluate if diarrhea occurs (5.6)
- Embryofoetal toxicity: Clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate (5.7)
- Exacerbation of myasthenia gravis (5.8)

ADVERSE REACTIONS
Most frequent adverse reactions for both adult and pediatric populations in clinical trials: abdominal pain, diarrhea, nausea, vomiting, dysgeusia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at 1-888-838-2872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Coadministration of clarithromycin can alter the concentrations of other drugs. The potential for drug-drug interactions must be considered prior to and during therapy. (4.5, 5.2, 5.4, 7)

USE IN SPECIFIC POPULATIONS
Geriatric: Increased risk of torsades de pointes (8.5)
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acute Bacterial Exacerbation of Chronic Bronchitis

Clarithromycin extended-release tablets are indicated in adults for the treatment of mild to moderate infections caused by susceptible isolates due to *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* [see Indications and Usage (1.9)].

1.2 Acute Maxillary Sinusitis

Clarithromycin extended-release tablets (in adults) are indicated for the treatment of mild to moderate infections caused by susceptible isolates due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* [see Indications and Usage (1.9)].

1.3 Community-Acquired Pneumonia

Clarithromycin extended-release tablets are indicated [see Indications and Usage (1.9)] for the treatment of mild to moderate infections caused by susceptible isolates due to:

- *Haemophilus influenzae* (in adults)
- *Haemophilus parainfluenzae* (in adults)
- *Moraxella catarrhalis* (in adults)
- *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Chlamydia pneumoniae* (in adults)

1.9 Limitations of Use

Clarithromycin extended-release tablets are indicated only for acute maxillary sinusitis, acute bacterial
exacerbation of chronic bronchitis, and community-acquired pneumonia in adults. The efficacy and safety of clarithromycin extended-release tablets in treating other infections for which clarithromycin immediate-release tablets and clarithromycin granules are approved have not been established.

There is resistance to macrolides in certain bacterial infections caused by *Streptococcus pneumoniae* and *Staphylococcus aureus*. Susceptibility testing should be performed when clinically indicated.

1.10 Usage

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Clarithromycin extended-release tablets should be taken with food. Swallow clarithromycin extended-release tablets whole; do not chew, break or crush clarithromycin extended-release tablets.

2.2 Adult Dosage

The recommended dosages of clarithromycin extended-release tablets for the treatment of mild to moderate infections in adults are listed in Table 1.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Dosage (every 24 hours)</th>
<th>Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute bacterial exacerbation of chronic bronchitis</td>
<td>1 gram</td>
<td>7</td>
</tr>
<tr>
<td>Acute maxillary sinusitis</td>
<td>1 gram</td>
<td>14</td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
<td>1 gram</td>
<td>7</td>
</tr>
</tbody>
</table>

2.6 Dosage Adjustment in Patients with Renal Impairment

See Table 2 for dosage adjustment in patients with moderate or severe renal impairment with or without concomitant atazanavir or ritonavir-containing regimens [see Drug Interactions (7)].

<table>
<thead>
<tr>
<th>Infection</th>
<th>Recommended Clarithromycin Dosage Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with severe renal impairment (CLcr of &lt;30 mL/min)</td>
<td>Reduce the dosage of Clarithromycin by 50%</td>
</tr>
<tr>
<td>Patients with moderate renal impairment (CLcr of 30 to 60 mL/min) taking concomitant atazanavir or ritonavir-containing regimens</td>
<td>Reduce the dosage of Clarithromycin by 50%</td>
</tr>
<tr>
<td>Patients with severe renal impairment (CLcr of &lt;30 mL/min) taking concomitant atazanavir or ritonavir-containing regimens</td>
<td>Reduce the dosage of Clarithromycin by 75%</td>
</tr>
</tbody>
</table>

2.7 Dosage Adjustment Due to Drug Interactions

Decrease the dose of clarithromycin by 50% when coadministered with atazanavir [see Drug Interactions (7)]. Dosage adjustments for other drugs when coadministered with clarithromycin may be recommended due to drug interactions [see Drug Interactions (7)].

3 DOSAGE FORMS AND STRENGTHS

Clarithromycin Extended-release Tablets USP (yellow, film coated, oval shaped, unscored tablets) are available as:

- 500 mg: debossed with △ and “777” on one side.
4 CONTRAINDICATIONS

4.1 Hypersensitivity
Clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, or any of the macrolide antibacterial drugs [see Warnings and Precautions (5.1)].

4.2 Cardiac Arrhythmias
Concomitant administration of clarithromycin with cisapride and pimozide is contraindicated [see Drug Interactions (7)].
There have been postmarketing reports of drug interactions when clarithromycin is coadministered with cisapride or pimozide, 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 clarithromycin. Fatalities have been reported.

4.3 Cholestatic Jaundice/Hepatic Dysfunction
Clarithromycin is contraindicated in patients with a history of cholestatic jaundice or hepatic dysfunction associated with prior use of clarithromycin.

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

4.5 HMG-CoA Reductase Inhibitors
Do not use clarithromycin 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 and Precautions (5.4) and Drug Interactions (7)].

4.6 Ergot Alkaloids
Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated [see Drug Interactions (7)].

4.7 Contraindications for Coadministered Drugs
For information about contraindications of other drugs indicated in combination with clarithromycin, refer to their full prescribing information (contraindications section).

5 WARNINGS AND PRECAUTIONS

5.1 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), Henoch-Schönlein purpura, and acute generalized exanthematous pustulosis, discontinue clarithromycin therapy immediately and institute appropriate treatment.

5.2 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.
Avoid clarithromycin in the following patients:
- patients with known prolongation of the QT interval, ventricular cardiac arrhythmia, including torsades de pointes
- patients receiving drugs known to prolong the QT interval [see also Contraindications (4.2)]
- patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia 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 [see Use in Specific Populations (8.5)].

5.3 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.

5.4 Serious Adverse Reactions Due to Concomitant Use with Other Drugs
Drugs metabolized by CYP3A4: 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...
Clarithromycin has demonstrated adverse effects on pregnancy outcome and/or embryo-fetal while the patient is taking this drug, the patient should be apprised of the potential hazard to the fetus. If clarithromycin is used during pregnancy, or if pregnancy occurs alternative therapy is appropriate. If clarithromycin is used during pregnancy, or if pregnancy occurs.

5.7 Embryofetal Toxicity

Clarithromycin is not an approved indication. The cause of the increased risk has not been established. Other epidemiologic studies evaluating this risk have shown variable results. Consider balancing this potential risk with the treatment benefits when prescribing clarithromycin in patients who have suspected or confirmed coronary artery disease.

5.5 All-Cause Mortality in Patients with Coronary Artery Disease 1 to 10 Years after Clarithromycin Exposure

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

5.6 Clostridium difficile Associated Diarrhea

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 antibacterial 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.

5.7 Embryofetal Toxicity

Clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If clarithromycin is used during pregnancy, or if pregnancy occurs while the patient is taking this drug, the patient should be apprised of the potential hazard to the fetus. Clarithromycin has demonstrated adverse effects on pregnancy outcome and/or embryo-fetal
development in monkeys, rats, mice, and rabbits at doses that produced plasma levels 2 times to 17 times the serum levels achieved in humans treated at the maximum recommended human doses [see Use in Specific Populations (8.1)].

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

5.9 Development of Drug Resistant Bacteria
Prescribing clarithromycin 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.

6 ADVERSE REACTIONS
The following serious adverse reactions are described below and elsewhere in the labeling:
- Acute Hypersensitivity Reactions [see Warnings and Precautions (5.1)]
- QT Prolongation [see Warnings and Precautions (5.2)]
- Hepatotoxicity [see Warnings and Precautions (5.3)]
- Serious Adverse Reactions Due to Concomitant Use with Other Drugs [see Warnings and Precautions (5.4)]
- Clostridium difficile Associated Diarrhea [see Warnings and Precautions (5.6)]
- Exacerbation of Myasthenia Gravis [see Warnings and Precautions (5.8)]

6.1 Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Based on pooled data across all indications, the most frequent adverse reactions for both adult and pediatric populations observed in clinical trials are abdominal pain, diarrhea, nausea, vomiting and dysgeusia. Also reported were dyspepsia, liver function test abnormal, anaphylactic reaction, candidiasis, headache, insomnia, and rash.

Gastrointestinal Adverse Reactions
In the acute exacerbation of chronic bronchitis and acute maxillary sinusitis studies overall gastrointestinal adverse reactions were reported by a similar proportion of patients taking either clarithromycin immediate-release tablets or clarithromycin extended-release tablets; however, patients taking clarithromycin extended-release tablets reported significantly less severe gastrointestinal symptoms compared to patients taking clarithromycin immediate-release tablets. In addition, patients taking clarithromycin extended-release tablets had significantly fewer premature discontinuations for drug-related gastrointestinal or abnormal taste adverse reactions compared to clarithromycin immediate-release tablets.

All-Cause Mortality in Patients with Coronary Artery Disease 1 to 10 Years Following Clarithromycin Exposure
In one clinical trial evaluating treatment with clarithromycin on outcomes in patients with coronary artery disease, an increase in risk of all-cause mortality was observed in patients randomized to clarithromycin. Clarithromycin for treatment of coronary artery disease is not an approved indication. Patients were treated with clarithromycin or placebo for 14 days and observed for primary outcome events (e.g., all-cause mortality or non-fatal cardiac events) for several years. 1 A numerically higher number of primary outcome events in patients randomized to receive clarithromycin was observed with a hazard ratio of 1.06 (95% confidence interval 0.98 to 1.14). However, at follow-up 10 years post-treatment, there were 866 (40%) deaths in the clarithromycin group and 815 (37%) deaths in the placebo group that represented a hazard ratio for all-cause mortality of 1.10 (95% confidence interval 1.00 to 1.21). The difference in the number of deaths emerged after one year or more after the end of treatment. The cause of the difference in all-cause mortality has not been established. Other epidemiologic studies evaluating this risk have shown variable results [see Warnings and Precautions (5.5)].

6.2 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: Thrombocytopenia, agranulocytosis
Cardiac: Ventricular arrhythmia, ventricular tachycardia, torsades de pointes
Ear and Labyrinth: Deafness was reported chiefly in elderly women and was usually reversible.
Gastrointestinal: 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:** Hepatic failure, jaundice hepatocellular. Adverse reactions related to hepatic dysfunction have been reported with clarithromycin [see Warnings and Precautions (5.2)].

**Infections and Infestations:** Pseudomembranous colitis [see Warnings and Precautions (5.6)]

**Immune System:** Anaphylactic reactions, angioedema

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

**Musculoskeletal and Connective Tissue:** Myopathy rhabdomyolysis was reported and in some of the reports, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol [see Contraindications (4.5) and Warnings and Precautions (5.4)].

**Nervous System:** Parosmia, anosmia, ageusia, paresthesia and convulsions

**Psychiatric:** Abnormal behavior, confusional state, depersonalization, disorientation, hallucination, depression, manic behavior, abnormal dream, psychotic disorder. These disorders usually resolve upon discontinuation of the drug.

**Renal and Urinary:** Nephritis interstitial, renal failure

**Skin and Subcutaneous Tissue:** Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), Henoch-Schonlein purpura, acne, acute generalized exanthematous pustulosis

**Vascular:** Hemorrhage

### 7 DRUG INTERACTIONS

Coadministration of clarithromycin is 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. Adjust dosage when 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. Adjust dosage when 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. Adjust dosage when 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. Adjust dosage when 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. Adjust dosage when 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. Adjust dosage when

<table>
<thead>
<tr>
<th><strong>Table 8: Clinically Significant Drug Interactions with Clarithromycin</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs That Are Affected By Clarithromycin</strong></td>
</tr>
<tr>
<td><strong>Antiarrhythmics:</strong> Disopyramide</td>
</tr>
</tbody>
</table>
| **Digoxin** | **Use With Caution** | | **Di**
| **Oral Anticoagulants:** Warfarin | **Oral anticoagulants:** 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 [see Warnings and Precautions (5.4)]. | Use With Caution | |
| **Antiepileptics:** Carbamazepine | **Carbamazepine:** 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. Increased serum concentrations of carbamazepine were observed in clinical trials with clarithromycin. There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with carbamazepine. | Use With Caution | |
| Antifungals: | Itraconazole | Use With Caution | Itraconazole: Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, potentially leading to a bi-directional drug interaction when administered concomitantly (see also Itraconazole under “Drugs That Affect Clarithromycin” in the table below). Clarithromycin may increase the plasma concentrations of itraconazole. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged adverse reactions.

| Fluconazole | No Dose Adjustment | Fluconazole [see Pharmacokinetics (12.3)]

| Anti-Gout Agents: | Colchicine (in patients with renal or hepatic impairment) | Contraindicated | Colchicine: Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (P-gp). Clarithromycin and other macrolides are known to inhibit CYP3A and P-gp. The dose of colchicine should be reduced when co-administered with clarithromycin in patients with normal renal and hepatic function [see Contraindications (4.4) and Warnings and Precautions (5.4)].

| | Colchicine (in patients with normal renal and hepatic function) | Use With Caution | Colchicine: Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (P-gp). Clarithromycin and other macrolides are known to inhibit CYP3A and P-gp. The dose of colchicine should be reduced when co-administered with clarithromycin in patients with normal renal and hepatic function [see Contraindications (4.4) and Warnings and Precautions (5.4)].

| Antipsychotics: | Pimozide | Contraindicated | Pimozide: [See Contraindications (4.2)]

| | Quetiapine | Use With Caution | Quetiapine: Quetiapine is a substrate for both CYP3A and saquinavir (as well as the efflux transporter P-gp). Clarithromycin and other macrolides are known to inhibit CYP3A and P-gp. There is evidence of a bi-directional drug interaction when co-administered. No dose adjustments are necessary for patients with normal renal function (see Selzentry ® prescribing information). See also Quetiapine under “Drugs that affect clarithromycin” in the table below) [see Pharmacokinetics (12.3)]

| Antispasmodics: | Tolterodine (patients deficient in CYP2D6 activity) | Use With Caution | 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 co-administered with clarithromycin.

| Antivirals: | Atazanavir | Use With Caution | Atazanavir: Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction (see Atazanavir under “Drugs That Affect Clarithromycin” in the table below) [see Pharmacokinetics (12.3)]

| | Saquinavir (in patients with decreased renal function) | Saquinavir: Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A and there is evidence of a bi-directional drug interaction (see Saquinavir under “Drugs That Affect Clarithromycin” in the table below) [see Pharmacokinetics (12.3)]

| | Ritonavir | Use With Caution | Ritonavir, Etravirine: [see Ritonavir and Etravirine under “Drugs That Affect Clarithromycin” in the table below) [see Pharmacokinetics (12.3)]

| | Maraviroc | Use With Caution | Maraviroc: Clarithromycin may result in increases in maraviroc exposures by inhibition of CYP3A metabolism. See Selzentry ® prescribing information for dose recommendation when given with strong CYP3A inhibitors such as clarithromycin.

| | Boceprevir (in patients with normal renal function) | No Dose Adjustment | Boceprevir: Both clarithromycin and boceprevir are substrates and inhibitors of CYP3A, potentially leading to a bi-directional drug interaction when co-administered. No dose adjustments are necessary for patients with normal renal function (see Victril ® prescribing information).

| | Didanosine | No Dose Adjustment | Didanosine: Simultaneous oral administration of clarithromycin immediate-release tablets and didanosine to HIV-infected adult patients may result in decreased steady-state didanosine concentrations. Administration of clarithromycin and didanosine should be separated by at least two hours [see Pharmacokinetics (12.3)]. The impact of co-administration of clarithromycin extended-release tablets or granules and didanosine has not been evaluated.

| | Zidovudine | Use With Caution | Zidovudine: Both clarithromycin and zidovudine have been observed in patients receiving concurrent zidovudine, [see Warnings and Precautions (5.4)].

| | Calcium Channel Blockers: | | Verapamil: Hypotension, bradycardia, and lactic acidosis have been observed in patients receiving concurrent verapamil, [see Warnings and Precautions (5.4)].

| | | | Amlodipine, Diltiazem [see Warnings and Precautions (5.4)]

| | | | Nifedipine: Nifedipine is a substrate for CYP3A. Clarithromycin and other macrolides are known to inhibit CYP3A. There is potential of CYP3A-mediated interaction between nifedipine and clarithromycin. Hypotension and peripheral edema were observed when clarithromycin was taken concurrently with nifedipine [see Warnings and Precautions (5.4)].

| | Ergot Alkaloids: | | 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 [see Contraindications (4.6)].

| | Gastroporokinetic Agents: | | Cisapride: [See Contraindications (4.2)]

| | HMG-CoA Reductase Inhibitors: | | Lovastatin, Simvastatin, Atorvastatin, Pravastatin, Fluvastatin [See Contraindications (4.5) and Warnings and Precautions (5.4)].
### Itraconazole

#### Antifungals:

**Pharmacokinetics of Drug(s) that Affect the Drugs that Affect Valproate Phenytoin Hexobarbital than CYP3A:**

**CYP450 Isoforms Other Drugs Metabolized by St. John's Wort**

- *Vinblastine*
- *Methylprednisolone*
- *Cilostazol*

**Other Drugs Metabolized by CYP450 Isoforms Other than CYP3A:**

- *Alfentanil*
- *Bromocriptine*
- *Cilostazol*
- *Methylprednisolone*
- *Vinblastine*
- *Phenobarbital*
- *St. John's Wort*

**Other Drugs Metabolized by CYP450 Isoforms Other than CYP3A:**

- *Hexobarbital*
- *Phenytin*
- *Valproate*

### Drugs that Affect Clarithromycin

<table>
<thead>
<tr>
<th>Drug(s) that Affect Clarithromycin</th>
<th>Recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungals: Itraconazole</td>
<td>Use With Caution</td>
<td>Itraconazole: 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 (see also Itraconazole under “Drugs That Affect Clarithromycin” in the table above).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atazanavir: When clarithromycin is co-administered with atazanavir, the dose of clarithromycin should be decreased by 50% [see Clinical Pharmacology (12.3)] . Since concentrations of 14-OH clarithromycin are significantly reduced when clarithromycin is co-</td>
</tr>
</tbody>
</table>
Adverse reactions were comparable in both groups. Adverse reactions occurred in 12.7% of infants exposed to clarithromycin were compared to 36 breastfed infants of mothers taking amoxicillin. Based on the average maternal weight of 64 kg, and less than 1% of the pediatric dose (15 mg/kg/day) 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, assuming milk consumption of 150 mL/kg/day, an exclusively human milk fed infant 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 antibacterial (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

### 8.3 Nursing Mothers

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.

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 antibacterial (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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Teratogenic Effects**

**Pregnancy Category C**

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 [see Warnings and Precautions (5.7)].

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 twice 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 twice 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 administered during gestation days 6 to 15 produced fetal growth retardation at plasma levels that were twice the human serum levels.

#### 8.2 Lactation

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.

Clarithromycin and its active metabolite 14-hydroxy clarithromycin are excreted in human milk. Based on the average maternal weight of 64 kg, and less than 1% of the pediatric dose (15 mg/kg/day) 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 antibacterial (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

### Table: Drug Interactions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Proton Pump Inhibitors: Omeprazole</th>
<th>Miscellaneous Cytchrome P450 Inducers: Efavirenz Nevirapine Rifampicin Rifabutin Rifapentine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use With Caution</td>
<td>Use With Caution</td>
<td>Use With Caution</td>
</tr>
<tr>
<td>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. There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with rifabutin (see Rifabutin under “Drugs That Are Affected By Clarithromycin” in the table above).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 12.3 Nursing Mothers

If pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus [see Warnings and Precautions (5.7)].

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 twice 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 twice 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 administered during gestation days 6 to 15 produced fetal growth retardation at plasma levels that were twice the human serum levels.

#### 8.4 Other Populations

**8.4.1 Children**

Clarithromycin should not be used in children under 2 years of age, unless in clinical circumstances where no alternative therapy is appropriate. If treatment is necessary, the patient should be apprised of the potential hazard to the fetus [see Warnings and Precautions (5.7)].

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 twice 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 twice 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 administered during gestation days 6 to 15 produced fetal growth retardation at plasma levels that were twice the human serum levels.

#### 8.4.2 Elderly

Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole [see Pharmacokinetics (12.3)].

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. There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with rifabutin (see Rifabutin under “Drugs That Are Affected By Clarithromycin” in the table above).
exposed to macrolides and included rash, diarrhea, loss of appetite, and somnolence.

8.4 Pediatric Use
The safety and effectiveness of clarithromycin extended-release tablets in the treatment of pediatric patients has not been established.

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.

8.5 Geriatric Use
In a steady-state study in which healthy elderly subjects (65 years to 81 years of age) were given 500 mg of clarithromycin 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 reactions when compared to younger patients. Consider dosage adjustment 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 (5.5)].

Most reports of acute kidney injury with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amiodipine, diltiazem, nifedipine) involved elderly patients 65 years of age or older [see Warnings and Precautions (5.4)].

Especially in elderly patients, there have been reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, some of which occurred in patients with renal insufficiency. Deaths have been reported in some patients [see Contraindications (4.4) and Warnings and Precautions (5.4)].

8.6 Renal and Hepatic Impairment
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 [see Dosage and Administration (2.6)].

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

Treat adverse reactions accompanying overdosage 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.

11 DESCRIPTION
Clarithromycin, USP is a semi-synthetic macrolide antimicrobial for oral use. Chemically, it is 6-O-methylerythromycin. The molecular formula is C_{38}H_{69}NO_{13}, and the molecular weight is 747.95. The structural formula is:

![Figure 1: Structure of Clarithromycin](image)

Clarithromycin, USP 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 unscored 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.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Clarithromycin is a macrolide antimicrobial drug [see Microbiology (12.4)].

12.3 Pharmacokinetics

Absorption

Clarithromycin Extended-Release Tablets

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 AUCs 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 tablets 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.

Figure 2: Steady-State Clarithromycin Plasma Concentration-Time Profiles

Distribution

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.

<p>| CONCENTRATION (after 250 mg every 12 hours) |</p>
<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Tissue (mcg/g)</th>
<th>Serum (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsil</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Lung</td>
<td>8.8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Metabolism and Elimination

Clarithromycin Extended-Release Tablets

In healthy human subjects, steady-state peak plasma clarithromycin concentrations of approximately 2 mcg/mL to 3 mcg/mL were achieved about 5 hours to 8 hours after oral administration of 1000 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 hours to 9 hours after dosing. Steady-state peak plasma clarithromycin concentrations of approximately 1 mcg/mL to 2 mcg/mL were achieved about 5 hours 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.

Specific Populations for Clarithromycin Extended-Release Tablets

HIV Infection

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-mg or 1000-mg doses of clarithromycin every 12 hours, steady-state clarithromycin C_{max} values ranged from
2 mcg/mL to 4 mcg/mL and 5 mcg/mL to 10 mcg/mL, respectively.

**Hepatic Impairment**

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.

**Renal Impairment**

The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function [see Use in Specific Populations (8.6) and Dosage and Administration (2.6)].

**Drug Interactions**

**Fluconazole**

Following administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers, the steady-state clarithromycin C<sub>max</sub> and AUC increased 33% and 18%, respectively. Clarithromycin exposures were increased and steady-state concentrations of 14-OH clarithromycin were not significantly affected by concomitant administration of fluconazole.

**Colchicine**

When a single dose of colchicine 0.6 mg was administered with clarithromycin 250 mg BID for 7 days, the colchicine C<sub>max</sub> increased 197% and the AUC<sub>0-∞</sub> increased 239% compared to administration of colchicine alone.

**Atazanavir**

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%.

**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.

**Saquinavir**

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<sub>max</sub> increased 177% and 187% respectively compared to administration of saquinavir alone. Clarithromycin AUC and C<sub>max</sub> increased 45% and 39% respectively, whereas the 14-OH clarithromycin AUC and C<sub>max</sub> decreased 24% and 34% respectively, compared to administration with clarithromycin alone.

**Didanosine**

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

**Zidovudine**

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<sub>max</sub> increased 100% whereas the AUC was unaffected (n=24).

**Omeprazole**

Clarithromycin 500 mg every 8 hours was given in combination with omeprazole 40 mg daily to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (C<sub>max</sub>, AUC<sub>0-24</sub>, and t<sub>1/2</sub> increases of 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin.

The plasma levels of clarithromycin and 14–OH clarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean C<sub>max</sub> was 10% greater, the mean C<sub>min</sub> was 27% greater, and the mean AUC<sub>0-24</sub> was 15% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14–OH clarithromycin, the mean C<sub>max</sub> was 45% greater, the mean C<sub>min</sub> was 57% greater, and the mean AUC<sub>0-24</sub> was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

| Clarithromycin Tissue Concentrations 2 hours after Dose (mcg/mL)/(mcg/g) |
|--------------------------------------------|----------------|----------------|----------------|----------------|
| Treatment                      | N  | antrum     | fundus    | N  | Mucus    |
| Clarithromycin                 |   | 10.48 ± 2.01 | 20.81 ± 7.64 |   | 4.15 ± 7.74 |
| Clarithromycin + Omeprazole    | 5  | 19.96 ± 4.71 | 24.25 ± 6.37 | 4  | 39.29 ± 32.79 |

**Theophylline**

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 C₁₀₀₀, C₅₀₀, and the area under the serum concentration–time curve (AUC) of theophylline increased about 20%.

**Midazolam**

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.

For information about other drugs indicated in combination with clarithromycin, refer to their full prescribing information, CLINICAL PHARMACOLOGY section.

**12.4 Microbiology**

**Mechanism of Action**

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

**Resistance**

The major routes of resistance are modification of the 23S rRNA in the 50S ribosomal subunit to insensitivity or drug efflux pumps. Beta-lactamase production should have no effect on clarithromycin activity.

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

**Antimicrobial Activity**

Clarithromycin has been shown to be active against most of the isolates of the following microorganisms both in vitro and in clinical infections [see Indications and Usage (1)]

**Gram-Positive Bacteria**
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

**Gram-Negative Bacteria**
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Moraxella catarrhalis*

**Other Microorganisms**
- *Chlamydia pneumoniae*
- *Helicobacter pylori*
- *Mycobacterium avium complex (MAC) consisting of M. avium and M. intracellularere*
- *Mycoplasma pneumoniae*

At least 90 percent of the microorganisms listed below exhibit in vitro minimum inhibitory concentrations (MICs) less than or equal to the clarithromycin susceptible MIC breakpoint for organisms of similar type to those shown in Table 11. However, the efficacy of clarithromycin in treating clinical infections due to these microorganisms has 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**
- *Legionella pneumophila*
- *Pasteurella multocida*

**Anaerobic Bacteria**
- *Clostridium perfringens*
- *Peptococcus niger*
- *Prevotella melaninogenica*
- *Propionibacterium acnes*

**Susceptibility Testing**

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

**13.1 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 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.

Impairment of Fertility
Fertility and reproduction studies have shown that daily doses of up to 160 mg/kg 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 twice the human serum levels. Testicular atrophy occurred in rats at doses 7 times, in dogs at doses 3 times, and in monkeys at doses 8 times greater than the maximum human daily dose (on a body surface area basis).

13.2 Animal Toxicology and/or Pharmacology
Corneal opacity occurred in dogs at doses 12 times and in monkeys at doses 8 times greater than the maximum human daily dose (on a body surface area basis). Lymphoid depletion occurred in dogs at doses 3 times greater than and in monkeys at doses 2 times greater than the maximum human daily dose (on a body surface area basis).

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING
Clarithromycin Extended-release Tablets USP are supplied as yellow, film coated, oval shaped, unscored tablets debossed with  and “777” on one side.
Bottles of 14 (NDC 43063-565-14).
Store clarithromycin extended-release tablets USP at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

17 PATIENT COUNSELING INFORMATION
Provide the following instructions or information about clarithromycin extended-release tablets to patients:

- Counsel patients 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 or other antibacterial drugs in the future.

- Advise patients that diarrhea is a common problem caused by antibacterials including clarithromycin extended-release tablets which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials, 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 antibacterial. If this occurs, instruct patients to contact their healthcare provider as soon as possible.

- Advise patients that clarithromycin extended-release tablets may interact with some drugs; therefore, advise patients to report to their healthcare provider the use of any other medications.

- Advise patients that clarithromycin extended-release tablets should be taken with food.

- There are no data on the effect of clarithromycin extended-release tablets on the ability to drive or use machines. However, counsel patients regarding the potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication. The potential for these adverse reactions should be taken into account before patients drive or use machines.

- Advise patients that if pregnancy occurs while taking this drug, there is a potential hazard to the fetus [see Warnings and Precautions (5.7) and Use in Specific Populations (8.1)].

- Advise patients who have coronary artery disease to continue medications and lifestyle modifications for their coronary artery disease because clarithromycin extended-release tablets may be associated with increased risk for mortality years after the end of clarithromycin treatment.

Brands listed are the trademarks of their respective owners.
### Product Information

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### Active Ingredient/Active Moiety

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### Inactive Ingredients

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### Product Characteristics

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**Patient First**

**CLARITHROMYCIN**
clarithromycin tablet, film coated, extended release

**WARNING KEEP OUT OF CHILDREN'S REACH**

**DISPENSE IN THIS TIGHT/LIGHT RESISTANT CONTAINER**

**AFFIX LABEL HERE**

Dosage and Storage: See package insert for a tight/light resistant container.

Do not use if pregnant. Take with food.

**AFFIX LABEL HERE**

MFG BY: ACTAVIS LABORATORIES FL, INC.
FORT LAUDERDALE, FL 33314 USA

Billing Number: 0591-2805
Packaged by PD-RX Pharmaceuticals, Inc.
Oklahoma City, OK 73132
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### Marketing Information

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<td>ANDA065145</td>
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**Labeler** - PD-Rx Pharmaceuticals, Inc. (156893695)

**Registrant** - PD-Rx Pharmaceuticals, Inc. (156893695)

### Establishment

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<th>Name</th>
<th>Address</th>
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<td>repack(43063-565)</td>
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Revised: 9/2018

PD-Rx Pharmaceuticals, Inc.