

Summary of Product Characteristics

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1. Name of the Medical Product

1.1 Product Name:

Claranta 250 (Clarithromycin Tablets USP 250 mg)

1.2 Strength:

Each film coated tablet contains
Clarithromycin USP 250 mg

1.3 Pharmaceutical Dosage Form:

Tablets

2. Qualitative & Quantitative Composition:

Each film coated tablet contains
Clarithromycin USP 250 mg

For a full list of excipients, see section 6.1

3. Pharmaceutical Form:

Yellow coloured circular, biconvex, film coated tablets.

4. Clinical Particulars

Therapeutic Indications:

Acute Bacterial Exacerbation of Chronic Bronchitis

Clarithromycin is 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*

Acute Maxillary Sinusitis

Clarithromycin are indicated for the treatment of mild to moderate infections caused by susceptible isolates due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*

Community-Acquired Pneumonia

Clarithromycin is indicated for the treatment of mild to moderate infections caused by susceptible isolates due to:

- *Haemophilus influenzae* (in adults)
- *Haemophilus parainfluenzae* (Clarithromycin in adults)
- *Moraxella catarrhalis* (Clarithromycin in adults)
- *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Chlamydophila pneumoniae* (Clarithromycin in adults and paediatric patients)

Pharyngitis/Tonsillitis

Clarithromycin is indicated for the treatment of mild to moderate infections caused by susceptible isolates due to *Streptococcus pyogenes* as an alternative in individuals who cannot use first line therapy.

Uncomplicated Skin and Skin Structure Infections

Clarithromycin is indicated for the treatment of mild to moderate infections caused by susceptible isolates due to *Staphylococcus aureus*, or *Streptococcus pyogenes*.

Acute Otitis Media

Clarithromycin is indicated in paediatric patients for the treatment of mild to moderate infections caused by susceptible isolates due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*

Treatment and Prophylaxis of Disseminated Mycobacterial Infections

Clarithromycin is indicated for the treatment of mild to moderate infections caused by susceptible isolates due to *Mycobacterium avium* or *Mycobacterium intracellulare* in patients with advanced HIV infection

***Helicobacter pylori* Infection and Duodenal Ulcer Disease**

Clarithromycin is given in combination with other drugs in adults as described below to eradicate *H. pylori*. The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence

- Clarithromycin in combination with amoxicillin and lansoprazole or omeprazole Delayed-Release Capsules, as triple therapy, are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or five-year history of duodenal ulcer) to eradicate *H. pylori*.
- Clarithromycin in combination with omeprazole capsules are indicated for the treatment of patients with an active duodenal ulcer associated with *H. pylori* infection. Regimens which contain Clarithromycin as the single antibacterial agent are more likely to be associated with the development of clarithromycin resistance among patients who fail therapy. Clarithromycin-containing regimens should not be used in patients with known or suspected clarithromycin resistant isolates because the efficacy of treatment is reduced in this setting.

Limitations of Use

Clarithromycin is indicated only for acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, and community-acquired pneumonia in adults. The efficacy and safety of Clarithromycin in treating other infections for which Clarithromycin is 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.

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.

Paediatric Use

The safety and effectiveness of clarithromycin have been established for the treatment of the following conditions or diseases in paediatric patients 6 months and older. Use in these indications is based on clinical trials in paediatric patients or adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in paediatric patients:

- Pharyngitis/Tonsillitis
- Community-Acquired Pneumonia
- Acute maxillary sinusitis
- Acute otitis media.
- Uncomplicated skin and skin structure infections

No studies of clarithromycin for MAC prophylaxis have been performed in pediatric populations and the doses recommended for prophylaxis are derived from MAC pediatric treatment studies.

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.

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

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

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

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.

4.2 Posology and Method of administration: Important Administration Instructions

Clarithromycin may be given with or without food.
 Clarithromycin should be taken with food. Swallow Clarithromycin whole; do not chew, break or crush Clarithromycin.

Adult Dosage

The recommended dosages of Clarithromycin for the treatment of mild to moderate infections in adults are listed in Table 1.

Table 1. Adult Dosage Guidelines

Infection	Clarithromycin		Clarithromycin	
	Dosage (every 12 hours)	Duration (days)	Dosage (every 24 hours)	Duration (days)
Acute bacterial exacerbation of chronic bronchitis	250 to 500 mg	7-14	1 gram	7
Acute maxillary sinusitis	500 mg	14	1 gram	14
Community-acquired pneumonia	250 mg	7-14	1 gram	7
Pharyngitis/Tonsillitis	250 mg	10	-	-
Uncomplicated skin and skin structure infections	250 mg	7-14	-	-
Treatment and prophylaxis of disseminated <i>Mycobacterium avium</i> disease [see Dosage and Administration (2.5)]	500 mg	-	-	-
<i>H. pylori</i> eradication to reduce the risk of duodenal ulcer recurrence with amoxicillin and omeprazole or lansoprazole [see Dosage and Administration (2.3)]	500 mg	10-14	-	-
<i>H. pylori</i> eradication to reduce the risk of duodenal ulcer recurrence with omeprazole [see Dosage and Administration (2.3)]	500 mg every 8 hours	14	-	-

a For *M. catarrhalis* and *S. pneumoniae* use 250 mg. For *H. influenzae* and *H. parainfluenzae*, use 500 mg. b For *H. parainfluenzae*, the duration of therapy is 7 days. c For *H. parainfluenzae* and *M. catarrhalis* use Clarithromycin tablets only. d For *H. influenzae*, the duration of therapy is 7 days. e Clarithromycin therapy should continue if clinical response is observed. Clarithromycin can be discontinued when the patient is considered at low risk of disseminated infection.

Combination Dosing Regimens for *H. pylori* Infection

- **Triple therapy: Clarithromycin /lansoprazole/amoxicillin**

The recommended adult dosage is 500 mg Clarithromycin, 30 mg lansoprazole, and 1 gram amoxicillin, all given every 12 hours for 10 or 14 days

- **Triple therapy: Clarithromycin /omeprazole/amoxicillin**

The recommended adult dosage is 500 mg Clarithromycin, 20 mg omeprazole, and 1 gram amoxicillin; all given every 12 hours for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief

- **Dual therapy: Clarithromycin /omeprazole**

The recommended adult dosage is 500 mg Clarithromycin given every 8 hours and 40 mg omeprazole given once every morning for 14 days. An additional 14 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief

Paediatric Dosage

The recommended daily dosage is 15 mg/kg/day divided every 12 hours for 10 days (up to the adult dose). Refer to dosage regimens for mycobacterial infections in paediatric patients for additional dosage information.

Dosage Regimens for Mycobacterial Infections

For the treatment of disseminated infection due to *Mycobacterium avium* complex (MAC), Clarithromycin are recommended as the primary agents. Clarithromycin should be used in combination with other anti-mycobacterial drugs (e.g. ethambutol) that have shown *in vitro* activity against MAC or clinical benefit in MAC treatment

Adult Patients

For treatment and prophylaxis of mycobacterial infections in adults, the recommended dose of Clarithromycin is 500 mg every 12 hours.

Paediatric Patients

For treatment and prophylaxis of mycobacterial infections in paediatric patients, the recommended dose is 7.5 mg/kg every 12 hours up to 500 mg every 12

hours Clarithromycin therapy should continue if clinical response is observed. Clarithromycin can be discontinued when the patient is considered at low risk of disseminated infection.

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

Table 2. Clarithromycin Dosage Adjustments in Patients with Renal Impairment

	Recommended Clarithromycin Dosage Reduction
Patients with severe renal impairment (CLcr of <30 mL/min)	Reduce the dosage of clarithromycin by 50%
Patients with moderate renal impairment (CLcr of 30 to 60 mL/min) taking concomitant atazanavir or ritonavir-containing regimens	Reduce the dosage of clarithromycin by 50%
Patients with severe renal impairment (CLcr of <30 mL/min) taking concomitant atazanavir or ritonavir-containing regimens	Reduce the dosage of clarithromycin by 75%

Dosage Adjustment Due to Drug Interactions

Decrease the dose of clarithromycin by 50 % when co-administered with atazanavir. Dosage adjustments for other drugs when co-administered with clarithromycin may be recommended due to drug interactions.

4.3 Contraindications:

Hypersensitivity

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

Cisapride and Pimozide

Concomitant administration of clarithromycin with cisapride and pimozide is contraindicated

There have been postmarketing reports of drug interactions when clarithromycin is co-administered 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.

Cholestatic Jaundice/Hepatic Dysfunction

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

Colchicine

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

Lomitapide, Lovastatin, and Simvastatin

Concomitant administration of clarithromycin with lomitapide is contraindicated due to potential for markedly increased transaminases. Concomitant administration of clarithromycin with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin) is contraindicated, due to the increased risk of myopathy, including rhabdomyolysis.

Ergot Alkaloids

Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated.

4.4 Special warning and precautions for use:

Severe 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-Schonlein purpura, and acute generalized exanthematous pustulosis, discontinue clarithromycin therapy immediately and institute appropriate treatment.

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
- patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia and in patients receiving Class IA (e.g., quinidine, procainamide, disopyramide) or Class III (e.g., dofetilide, amiodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval

Hepatotoxicity

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. 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.

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; markedly increased transaminases with lomitapide; rhabdomyolysis with simvastatin, lovastatin, and atorvastatin; hypoglycemia and cardiac arrhythmias (e.g., *torsades de pointes*) 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. Use clarithromycin with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme. The use of clarithromycin with lomitapide, simvastatin, lovastatin, ergotamine, or dihydroergotamine is contraindicated

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 co-administration of clarithromycin and colchicine is necessary in patients with normal renal and hepatic function, reduce the dose of colchicine. Monitor patients for clinical symptoms of colchicine toxicity. Concomitant administration of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment

Lomitapide: Concomitant use of clarithromycin with lomitapide is contraindicated. Lomitapide is metabolized by CYP3A4, and concomitant treatment with clarithromycin increases the plasma concentration of lomitapide, which increases the risk of elevation in transaminases. If treatment with clarithromycin cannot be avoided, therapy with lomitapide must be suspended during the course of treatment.

HMG-CoA Reductase Inhibitors (statins): Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolized by CYP3A4, and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. 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.

Exercise caution when prescribing clarithromycin with atorvastatin or pravastatin. 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.

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

Quetiapine: Use quetiapine and clarithromycin concomitantly with caution. Co-administration 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 co-administered with CYP3A4 inhibitors such as clarithromycin

Oral Anticoagulants: There is a risk of serious hemorrhage and significant elevations in INR and prothrombin time when clarithromycin is co-administered with warfarin. Monitor INR and prothrombin times frequently while patients are receiving clarithromycin and oral anticoagulants concurrently

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

All-Cause Mortality in Patients with Coronary Artery Disease 1to10 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.¹ 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.

***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 antibacterial 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, antibacterial treatment of *C. difficile*,

and surgical evaluation should be instituted as clinically indicated.

Embryo-Fetal Toxicity

Based on findings from animal studies, clarithromycin is not recommended for use 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 demonstrated adverse effects on pregnancy outcome and/or embryo fetal development, including fetal malformations, in pregnant animals administered oral clarithromycin.

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.

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.

4.5 Interactions with other medicinal products and other forms of Interactions:

Co-administration 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 appropriate and monitor serum concentrations of drugs primarily metabolized by CYP3A closely in patients concurrently receiving clarithromycin.

Table 8: Clinically Significant Drug Interactions with clarithromycin

Drugs That Are Affected By clarithromycin		
Drug(s) with Pharmacokinetics Affected by Clarithromycin	Recommendation	Comments
Antiarrhythmics: Disopyramide Quinidine Dofetilide Amiodarone Sotalol Procainamide	Not Recommended	Disopyramide, Quinidine: There have been post marketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during

		coadministration of clarithromycin with these drugs Serum concentrations of these medications should also be monitored. There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with disopyramide and quinidine. 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.
Digoxin	Use with Caution	Digoxin: Digoxin is a substrate for P-glycoprotein (Pgp) and clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are co-administered, 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 post marketing 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.
Oral Anticoagulants: Warfarin	Use with Caution	Oral anticoagulants: Spontaneous reports in the post marketing 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
Antiepileptics: Carbamazepine	Use with Caution	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.
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. Clarithromycin may increase the plasma concentrations of itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged adverse reactions.
Anti-Gout Agents: Colchicine (in patients with renal or hepatic impairment) Colchicine (in patients with normal renal and hepatic function)	Contraindicated Use with Caution	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. The dose of colchicine should be reduced when co-administered with clarithromycin in patients with normal renal and hepatic function.
Antipsychotics: Pimozide, quetiapine	Contraindicated	Quetiapine is a substrate for CYP3A4, which is inhibited by clarithromycin. Co-administration 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 co-administered with CYP3A4 inhibitors such as clarithromycin.
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 Saquinavir (in patients with decreased renal function) Saquinavir: Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A and their function) Ritonavir Etravirine Maraviroc Boceprevir (in patients with normal renal function) Didanosine Zidovudine	Use with Caution No Dose Adjustment	Atazanavir: Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction Saquinavir: Both clarithromycin and saquinavir with decreased renal function) is evidence of a bi-directional drug interaction 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: 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 Zidovudine: Simultaneous oral administration of clarithromycin immediate-release tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Administration of clarithromycin and zidovudine should be separated by at least two hours The impact of co-administration of clarithromycin extended-release tablets or granules and zidovudine has not been evaluated.
Calcium Channel Blockers: Verapamil Amlodipine Diltiazem Nifedipine	Use with Caution	Verapamil: Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil 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 concomitantly with nifedipine
Ergot Alkaloids: Ergotamine Dihydroergotamine	Contraindicated	Ergotamine, Dihydroergotamine: Post marketing reports indicate that coadministration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia

		of the extremities and other tissues including the central nervous system
Gastroprokinetic Agents: Cisapride	Contraindicated	Cisapride
Lipid-lowering agents: Lomitapide Lovastatin Simvastatin Atorvastatin Pravastatin Fluvastatin	Contraindicated	Lomitapide, Lovastatin, Simvastatin: Clarithromycin may increase the exposure of these drugs by inhibition of CYP3A metabolism, thereby increasing the risk of toxicities from these drugs
Hypoglycemic Agents: Nateglinide Pioglitazone Repaglinide Rosiglitazone Insulin	Use with Caution	Nateglinide, Pioglitazone, Repaglinide, Rosiglitazone Insulin
Phosphodiesterase inhibitors: Sildenafil Tadalafil Vardenafil	Use with Caution	Sildenafil, Tadalafil, Vardenafil: Each of these phosphodiesterase inhibitors is primarily metabolized by CYP3A, and CYP3A will be inhibited by concomitant administration of clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil, or vardenafil will result in increased exposure of these phosphodiesterase inhibitors. Co-administration of these phosphodiesterase inhibitors with clarithromycin is not recommended. Increased systemic exposure of these drugs may occur with clarithromycin; reduction of dosage for phosphodiesterase inhibitors should be considered
Proton Pump Inhibitors: Omeprazole	No Dose Adjustment	Omeprazole: The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when co-administered with clarithromycin as a result of increased omeprazole exposures
Xanthine Derivatives: Theophylline	Use with Caution	Theophylline: 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.

Triazolobenzodiazepines and Other Related Benzodiazepines: Midazolam Alprazolam Triazolam Temazepam Nitrazepam Lorazepam	Use with Caution	Midazolam: When oral midazolam is co-administered with clarithromycin, dose adjustments may be necessary and possible prolongation and intensity of effect should be anticipated Triazolam, Alprazolam: Caution and appropriate dose adjustments should be considered when triazolam or alprazolam is co-administered with clarithromycin. There have been post marketing reports of drug interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested. In post marketing experience, erythromycin has been reported to decrease the clearance of triazolam and midazolam, and thus, may increase the pharmacologic effect of these benzodiazepines. Temazepam, Nitrazepam, Lorazepam: For benzodiazepines which are not metabolized by CYP3A (e.g., temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.
Cytochrome P450 Inducers: Rifabutin	Use with Caution	Rifabutin: 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
Other Drugs Metabolized by CYP3A: Alfentanil Bromocriptine Cilostazol Methylprednisolone Vinblastine Phenobarbital St. John's Wort	Use with Caution	There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with alfentanil, methylprednisolone, cilostazol, bromocriptine, vinblastine, phenobarbital, and St. John's Wort
Other Drugs Metabolized by CYP450 Isoforms Other than CYP3A: Hexobarbital Phenytoin Valproate	Use with Caution	There have been post marketing reports of interactions of clarithromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.
Drugs that Affect clarithromycin		
Drug(s) that Affect the Pharmacokinetics of clarithromycin	Recommendation	Comments
Antifungals: Itraconazole	Use with Caution	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
Antivirals: Atazanavir	Use with Caution	Atazanavir: When clarithromycin is co-administered with atazanavir, the dose of clarithromycin should be decreased by 50%. Since concentrations of 14-OH clarithromycin are significantly reduced when clarithromycin is co-administered with atazanavir, alternative antibacterial therapy should be considered for indications other than infections due to Mycobacterium avium complex. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.
Ritonavir (in patients with decreased renal function)	Use with Caution	Ritonavir: Since concentrations of 14-OH clarithromycin are significantly reduced when clarithromycin is co-administered with ritonavir, alternative antibacterial therapy should be considered for indications other than infections due to Mycobacterium avium
Saquinavir (in patients with decreased renal function)	Use with Caution	Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors. Saquinavir: When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (refer to ritonavir above)
Etravirine	Use with Caution	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.
Saquinavir (in patients with normal renal function) Ritonavir (in patients with normal renal function)	Use with Caution	
Proton Pump Inhibitors: Omeprazole	Use with Caution	Omeprazole: Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole
Miscellaneous	Use with	Inducers of CYP3A enzymes, such as

Cytochrome P450 Inducers: Efavirenz Nevirapine Rifampicin Rifabutin Rifapentine	Caution	efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine will increase the metabolism of clarithromycin, thus decreasing plasma concentrations of clarithromycin, while increasing those of 14-OHclarithromycin. Since the microbiological activities of clarithromycin and 14-OHclarithromycin 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
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4.6 Fertility, pregnancy, and lactation:

Pregnancy

Risk Summary

Based on findings from animal studies, clarithromycin is not recommended for use in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking clarithromycin, the patient should be apprised of the potential hazard to the fetus.

Lactation

Risk Summary

Based on limited human data, clarithromycin and its active metabolite 14-OH clarithromycin are present in human milk at less than 2% of the maternal weight-adjusted dose (see Data). In a separate observational study, reported adverse effects on breast-fed children (rash, diarrhea, loss of appetite, somnolence) were comparable to amoxicillin (see Data). No data are available to assess the effects of clarithromycin or 14-OH clarithromycin on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for clarithromycin and any potential adverse effects on the breast-fed child from clarithromycin or from the underlying maternal condition.

Females and Males of Reproductive Potential

Males

Administration of clarithromycin resulted in testicular atrophy in rats, dogs and monkeys.

4.7 Effects on ability to drive and use machine:

Data not available.

4.8 Undesirable Effects:

The following serious adverse reactions are described below and elsewhere in the labeling:

- Acute Hypersensitivity Reactions

- QT Prolongation
- Hepatotoxicity
- Serious Adverse Reactions Due to Concomitant Use with Other Drugs
- *Clostridium difficile* Associated Diarrhea
- Exacerbation of Myasthenia Gravis

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.

The subsequent subsections list the most common adverse reactions for prophylaxis and treatment of mycobacterial infections and duodenal ulcer associated with *H. pylori* infection. In general, these profiles are consistent with the pooled data described above.

Prophylaxis of Mycobacterial Infections

In AIDS patients treated with clarithromycin over long periods of time for prophylaxis against *M. avium*, it was often difficult to distinguish adverse reactions possibly associated with clarithromycin administration from underlying HIV disease or intercurrent illness. Median duration of treatment was 10.6 months for the clarithromycin group and 8.2 months for the placebo group.

Incidence Rates (%) of Selected Adverse Reactions in Immunocompromised Adult Patients Receiving Prophylaxis Against *M. avium* Complex

Body System Adverse Reaction	Clarithromycin (n=339) %	Placebo (n=339) %
Body as a whole		
Abdominal Pain	5%	4%
Headache	3%	1%
Digestive		
Diarrhea	8%	4%
Dyspepsia	4%	3%
Flatulence	2%	1%
Nausea	11%	7%
Vomiting	6%	3%
Skin & Appendages		
Rash	3%	4%

Special Senses		
Taste Perversion	8%	0.3%

a Includes those events possibly or probably related to study drug and excludes concurrent conditions

b 2% or greater Adverse Reaction Incidence Rates for either treatment group

c Significant higher incidence compared to the placebo-treated group

Discontinuation due to adverse reactions occurred in 18% of patients receiving clarithromycin compared to 17% of patients receiving placebo in this trial. Primary reasons for discontinuation in clarithromycin treated patients include headache, nausea, vomiting, depression, and taste perversion.

Changes in Laboratory Values

Selected laboratory adverse experiences that were reported during therapy in greater than 2 % of adult patients treated with clarithromycin in a randomized double-blind clinical trial involving 682 patients are presented in Table 5.

In immunocompromised patients receiving prophylaxis against *M. avium*, evaluations of laboratory values were made by analyzing those values outside the seriously abnormal value (i.e., the extreme high or low limit) for the specified test.

Percentage of Patients^a Exceeding Extreme Laboratory Values in Patients Receiving Prophylaxis Against *M. avium* Complex

		Clarithromycin 500mg twice a day	Placebo
WBC count	<1 x 10 ⁹ /L	2/103 (4%)	0/95
SGOT	>5 x ULN ^b	7/196 (4%)	5/208 (2%)
SGPT	>5 x ULN ^b	6/217 (3%)	4/232 (2%)
a Includes only patients with baseline values within the normal range or borderline high (hematology variables) and within normal range or borderline low (chemistry variables)			
b ULN= Upper Limit of Normal			

The adverse reaction profiles for both the 500 mg and 1000 mg twice a day dose regimen was similar.

In AIDS patients and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse reactions possibly associated with clarithromycin administration from underlying signs of HIV disease or intercurrent illness.

The following analysis summarizes experience during the first 12 weeks of therapy with clarithromycin. Data are reported separately for trial 1 (randomized, double-blind) and trial 2 (openlabeled, compassionate use) and also combined. Adverse reactions were reported less frequently in trial 2, which may be due in part to differences in monitoring between the two studies.

In adult patients receiving clarithromycin 500 mg twice a day, the most frequently reported adverse reactions, considered possibly or possibly related to study drug, with an incidence of 5% or greater, are listed below (Table 6). Approximately 8% of the patients who received 500 mg twice a day and 12% of

the patients who received 1000 mg twice a day discontinued therapy due to drug related adverse reactions during the first 12 weeks of therapy; adverse reactions leading to discontinuation in at least 2 patients included nausea, vomiting, abdominal pain, diarrhea, rash, and asthenia.

Selected Treatment-Related^a Adverse Reaction Incidence Rates(%) in Immunocompromised Adult Patients During the First 12 Weeks of Therapy with 500mg Twice a Day clarithromycin Dose

Adverse Reaction	Trial 1 (n=53)	Trial 2 (n=255)	Combined (n=308)
Abdominal Pain	8	2	3
Diarrhea	9	2	3
Flatulence	8	0	1
Headache	8	0	2
Nausea	28	9	12
Rash	9	2	3
Taste Perversion	19	0	4
Vomiting	25	4	8
^a Includes those events possibly or probably related to study drug and excludes concurrent conditions			

A limited number of pediatric AIDS patients have been treated with clarithromycin suspension for mycobacterial infections. The most frequently reported adverse reactions excluding those due to the patient's concurrent conditions were consistent with those observed in adult patients.

Changes in Laboratory Values

In the first 12 weeks of starting on clarithromycin 500 mg twice a day, 3% of patients has SGOT increases and 2% of patients has SGPT increases > 5 times the upper limit of normal in trial 2 (469 enrolled adult patients) while trial 1 (154 enrolled patients) had no elevation of transaminases. This includes only patients with baseline values within the normal range or borderline low.

Duodenal ulcer associated with *H. pylori* Infection

In clinical trials using combination therapy with clarithromycin plus omeprazole and amoxicillin, no adverse reactions specific to the combination of these drugs have been observed. Adverse reactions that have occurred have been limited to those that have been previously reported with clarithromycin, omeprazole or amoxicillin.

The adverse reaction profiles are shown below (Table 7) for four randomized double-blind clinical trials in which patients received the combination of clarithromycin 500 mg three times a day, and omeprazole 40 mg daily for 14 days, followed by omeprazole 20 mg once a day, (three studies) or 40 mg once a day (one study) for an additional 14 days. Of the 346 patients who received the combination, 3.5% of patients discontinued drug due to adverse reactions.

Adverse Reactions with an Incidence of 3% or Greater

Adverse Reaction	BIAXIN + Omeprazole (n=346) % of Patients	Omeprazole (n=355) % of Patients	BIAXIN (n=166) % of Patients ^a
Taste Perversion	15	1	16
Nausea	5	1	3
Headache	5	6	9
Diarrhea	4	3	7
Vomiting	4	<1	1
Abdominal Pain	3	2	1
Infection	3	4	2
^a Only two of four studies			

Changes in Laboratory Values

Changes in laboratory values with possible clinical significance in patients taking clarithromycin and omeprazole in four randomized double-blind trials in 945 patients are as follows:

Hepatic: elevated direct bilirubin <1%; GGT <1%; SGOT (AST) <1%; SGPT (ALT) <1%,

Renal: elevated serum creatinine <1%.

Less Frequent Adverse Reactions Observed During Clinical Trials of Clarithromycin

Based on pooled data across all indications, the following adverse reactions were observed in clinical trials with clarithromycin at a rate less than 1%:

Blood and Lymphatic System Disorders: Leukopenia, neutropenia, thrombocytopenia, 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

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

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.

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 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

Infections and Infestations: Pseudomembranous colitis.

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

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

Reporting of suspected adverse reactions: Healthcare professional are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS)
<https://pv.pharmacyboardkenya.org>.

4.9 Overdose:

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.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Antimicrobials in systemic use, Macrolides
ATC code: J01FA09.

Mechanism of action

Clarithromycin is a macrolide antimicrobial drug.

5.2 Pharmacokinetic properties:

Absorption

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 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 may be given without regard to food. In non-fasting healthy human subjects (males and females), peak plasma concentrations were attained within 2 to 3 hours after oral dosing.

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.

Metabolism and Elimination

Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 1 mcg/mL to 2 mcg/mL with a 250 mg dose administered every 12 hours and 3 mcg/mL to 4 mcg/mL with a 500 mg dose administered every 8 hours to 12 hours. The elimination half-life of clarithromycin was about 3 hours to 4 hours with 250 mg administered every 12 hours but increased to 5 hours to 7 hours with 500 mg administered every 8 hours to 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 8 hours 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 hours to 6 hours. With a 500 mg every 8 hours 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 hours to 9 hours. With any of these dosing regimens, the steady-state concentration of this metabolite is generally attained within 3 days 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.

5.3 Preclinical safety data:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenesis

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/day 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).

6. Pharmaceutical particulars:

6.1 List of excipients

Microcrystalline Cellulose, Povidone, Carmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Instacoat Aqua-III (IA-III-40474), Purified Water.

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

36 months

6.4 Special Precautions for storage:

Store at temperature below 30°C. Protect from light.

6.5 Nature and contents of container:

10 tablets in a blister pack, 2 blisters in a printed carton along with pack insert.

6.6 Special precautions for disposal and other handling:

Not applicable

7. Marketing authorization holder and manufacturing site addresses:**Marketing authorization holder:**

Ajanta Pharma Limited
Ajanta House,
Charkop, Kandivli (West),
Mumbai- 400 067,
India

Manufacturing Site Address:

Ajanta Pharma Limited
Plot No. B-4/5/6, MIDC, Paithan,
Chhatrapati Sambhajnagar 431148
Maharashtra State, India.

8. Marketing authorization number: H2013/19214/124

9. Date of first registration/ renewal of the registration:

Date of first registration: Jul 08, 2013

10. Date of revision of text: May, 2026