PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrTARO-CLARITHROMYCIN

Clarithromycin for Oral Suspension
Powder for Suspension, 125 mg/5 mL and 250 mg/5 mL when reconstituted, Oral
USP

Antibiotic

NOTE: WHEN USED IN COMBINATION WITH ACID ANTISECRETORY DRUGS AND OTHER ANTIMICROBIALS FOR THE ERADICATION OF HELICOBACTER PYLORI, THE PRODUCT MONOGRAPH FOR THOSE AGENTS SHOULD BE CONSULTED.

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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	11/2022
7 WARNINGS AND PRECAUTIONS; 7.1.1 Pregnant Women; 7.1.2 Breast-feeding	11/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Taro-Clarithromycin (Clarithromycin for Oral Suspension, USP)

Taro-Clarithromycin (Clarithromycin for Oral Suspension, USP) is indicated for the treatment of infections due to susceptible organisms, in the following conditions:

- Upper Respiratory Tract
  - Pharyngitis caused by *S. pyogenes* (Group A β-hemolytic streptococci).
  - Acute otitis media caused by *H. influenzae*, *M. catarrhalis*, or *S. pneumoniae.* See **14 CLINICAL TRIALS, Otitis Media**.

- Lower Respiratory Tract
  - Mild to moderate community-acquired pneumonia caused by *S. pneumoniae*, *C. pneumoniae*, or *M. pneumoniae*. See **7 3 SERIOUS WARNINGS** AND PRECAUTIONS, **Sensitivity/Resistance**.

- Uncomplicated skin and skin structure infections
  - Uncomplicated skin and skin structure infections (i.e., impetigo and cellulitis) caused by *S. aureus or S. pyogenes*. See **7 3 SERIOUS WARNINGS** AND PRECAUTIONS, **Sensitivity/Resistance**.

- Mycobacterial Infections
  - Disseminated mycobacterial infections due to *M. avium* and *M. intracellulare.*

To reduce the development of drug-resistant bacteria and maintain the effectiveness of clarithromycin for oral suspension and other antibacterial drugs, Taro-Clarithromycin (Clarithromycin for oral suspension) should be used only to treat 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.

1.1 Pediatrics

Pediatrics (6 months - 12 years of age): Dosing recommendations for children are based on body weight. See **7 WARNINGS AND PRECAUTIONS**, **7.1 Special Populations**, **7.1.3 Pediatrics** and **4 DOSAGE AND ADMINISTRATION**, **Table 1**.

1.2 Geriatrics

Geriatrics (> 65 years of age): Dosage adjustment should be considered in elderly patients with severe renal impairment. See **7 WARNINGS AND PRECAUTIONS**, **7.1 Special Populations, 7.1.4 Geriatrics.**

2 CONTRAINDICATIONS

Taro-Clarithromycin (clarithromycin for oral suspension, USP) is contraindicated in

- Patients with a known hypersensitivity to clarithromycin, erythromycin, other macrolide antibacterial agents or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. See **6 DOSAGE FORMS**, **COMPOSITION AND PACKAGING**.

- Patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of clarithromycin.

- Patients who suffer from severe hepatic failure in combination with renal impairment. See **7 3 SERIOUS WARNINGS** AND PRECAUTIONS, **Hepatic/Biliary/Pancreatic, 7 3 SERIOUS WARNINGS** AND PRECAUTIONS**, Renal, 4** Error! Reference source not found.**, Dosing Considerations** and **4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**.

- Patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes. See **7 WARNINGS AND PRECAUTIONS** and **9 DRUG INTERACTIONS, Drug-Drug Interactions**.

- Patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of QT interval and torsades de pointes).

- Concomitant therapy with astemizole, cisapride, domperidone, pimozide, terfenadine.

  There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with astemizole, cisapride, pimozide or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of hepatic metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported. See **9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4.**

- Concomitant therapy with saquinavir due to potentially life-threatening cardiac arrhythmia.

- Concomitant therapy with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin), due to an increased risk of myopathy, including rhabdomyolysis. See **9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4.**

- Concomitant therapy with ergot alkaloids (e.g., ergotamine or dihydroergotamine) as this may result in ergot toxicity. See **9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4**.

- Concomitant administration with oral midazolam. See **9 9 DRUG** INTERACTIONS, **9.3 Drug-Behavioural Interactions**

This information is not available for this drug product.

9.4 Drug-Drug Interactions**, 4.**

- Concomitant therapy with colchicine due to the risk of life threatening and fatal colchicine toxicity. This risk may be further increased with concomitant medications metabolized by P-glycoprotein or strong CYP3A inhibitors. See **9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4.**

- concomitant therapy with ticagrelor or ranolazine*.

*Not marketed in Canada

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Clarithromycin should not be used in **pregnancy**, particularly during the first 3 months of pregnancy. See **7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women**.

- The concomitant administration of clarithromycin and drugs metabolized by CYP3A and/or transported by P-gp may result in significant safety concerns. See **7 WARNINGS AND PRECAUTIONS** and **9 DRUG INTERACTIONS, 9.2 Drug Interactions Overview**.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Taro-Clarithromycin (Clarithromycin for Oral suspension, USP) may be given with or without meals.
- In patients with a combination of hepatic (mild to moderate) and renal impairments or in the presence of severe renal impairment, decreased dosage of clarithromycin or prolonged dosing intervals might be appropriate. See **4** Error! Reference source not found.**, 4.2 Recommended Dose and Dosage Adjustment**.
- Clarithromycin is contraindicated in patients with severe hepatic failure in combination with renal impairment. See **2 2** CONTRAINDICATIONS.

- In children with renal impairment and a creatinine clearance < 30 mL/min, the dosage of Taro-Clarithromycin should be reduced by one-half, i.e., up to 250 mg once daily, or 250 mg twice daily in more severe infections. Dosage should not be continued beyond 14 days in these patients.

4.2 Recommended Dose and Dosage Adjustment

Taro-Clarithromycin (Clarithromycin for Oral Suspension, USP)

- The recommended daily dosage of Taro-Clarithromycin (clarithromycin for oral suspension, USP) is 15 mg/kg/day, in divided doses every 12 hours, not to exceed 1000 mg/day. The usual duration of treatment is for 5 to 10 days depending on the pathogen involved and the severity of the condition. Treatment for pharyngitis caused by *Streptococcal* species should be 10 days.
- In children with renal impairment and a creatinine clearance < 30 mL/min, the dosage of Taro-Clarithromycin (Clarithromycin for Oral Suspension, USP) should be reduced by one-half, i.e., up to 250 mg once daily, or 250 mg twice daily in more severe infections. Dosage should not be continued beyond 14 days in these patients.
- Error! Reference source not found. is a suggested guide for determining dosage.

Table 1:
Taro-Clarithromycin (Clarithromycin for Oral Suspension, USP)
Pediatric Dosage Guidelines
Based on Body Weight in kg

	125 mg/5 mL	250 mg/5 mL
Weight*	**Dosage (mL) given twice daily**	**Dosage (mL) given twice daily**
8 to 11 kg (1 to 2 years)**	2.5	1.25
12 to 19 kg (2 to 4 years)	5	2.5
20 to 29 kg (4 to 8 years)	7.5	3.75
30 to 40 kg (8 to 12 years)	10	5

*** Children < 8 kg should be dosed on a per kg basis (approximately 7.5 mg/kg twice daily).**
****Approximate ages.**

- **Children with Mycobacterial Infections**
  - Clarithromycin is recommended as the primary agent for the treatment of disseminated infection due to MAC. Clarithromycin should be used in combination with other antimycobacterial drugs which have shown *in vitro* activity against MAC, including ethambutol and rifampin. Although no controlled clinical trial information is available for combination therapy with clarithromycin, the U.S. Public Health Service Task Force has provided recommendations for the treatment of MAC.
  - In children, the recommended dose is 7.5 mg/kg twice daily up to 500 mg twice daily clarithromycin per day in 2 divided doses. Dosing recommendations for children are shown in **Table 1** above.
  - Treatment of disseminated MAC infections in AIDS patients should continue for life if clinical and mycobacterial improvement are observed.

4.3 Reconstitution

Oral Solutions:

- Directions for Reconstitution: 125 mg/5 mL
    - 55 mL size: Measure the required volume (35 mL) of water using a graduated cylinder. Add half the volume of water to the bottle and shake vigorously. Add the remainder of water to the bottle and shake. When reconstituted as directed, each teaspoonful (5 mL) contains: Clarithromycin 125 mg in a fruity-flavored, aqueous vehicle.
    - 105 mL size: Measure the required volume (64 mL) of water using a graduated cylinder. Add half the volume of water to the bottle and shake vigorously. Add the remainder of water to the bottle and shake. When reconstituted as directed, each teaspoonful (5 mL) contains: Clarithromycin 125 mg in a fruity-flavored, aqueous vehicle.
    - 150 mL size: Measure the required volume (91 mL) of water using a graduated cylinder. Add half the volume of water to the bottle and shake vigorously. Add the remainder of water to the bottle and shake. When reconstituted as directed, each teaspoonful (5 mL) contains: Clarithromycin 125 mg in a fruity-flavored, aqueous vehicle.

- Directions for Reconstitution: 250 mg/5 mL
    - 105 mL size: Measure the required volume (64 mL) of water using a graduated cylinder. Add half the volume of water to the bottle and shake vigorously. Add the remainder of water to the bottle and shake. When reconstituted as directed, each teaspoonful (5 mL) contains: Clarithromycin 250 mg in a fruity-flavored, aqueous vehicle.

Shake until all the particles are suspended. Avoid vigorous and/or lengthy shaking. Shake prior to each subsequent use to ensure resuspension. After reconstitution, store between (15ºC and 25ºC) and use within 14 days. Do not refrigerate. . Any reconstituted unused medication should be discarded after 14 days. The graduated syringe used for dosage administration should be rinsed between uses. Do not leave syringe in bottle. Do not store reconstituted suspension in syringe. See **11 STORAGE, STABILITY AND DISPOSAL.**

4.4 Administration

Taro-Clarithromycin (Clarithromycin for Oral Suspension, USP) sometimes has a bitter after taste, therefore, the suspension should be taken with food and/or juice.

4.5 Missed Dose

If a dose of clarithromycin is missed, the patient should take the dose as soon as possible and then return to their normal scheduled dose. However, if a dose is skipped, the patient should not double the next dose.

5 OVERDOSAGE

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures.

Clarithromycin is protein bound (70%). No data are available on the elimination of clarithromycin by hemodialysis or peritoneal dialysis.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	oral suspension / 125 mg / 5 mL and 250 mg / 5 mL	acetone, alginic acid, aspartame, castor oil, citric acid (anhydrous), colloidal silicon dioxide, croscarmellose sodium, flavour peppermint, flavour tutti frutti, hydroxypropyl cellulose, hypromellose, hypromellose phthalate, maltodextrin, povidone, sodium benzoate, sodium chloride, sodium citrate (dihydrate), sucrose, titanium dioxide and xanthan gum.

Taro-Clarithromycin (Clarithromycin for Oral Suspension, USP) 125 mg/5 mL is supplied as a granular preparation in 55 mL, 105 mL, and 150 mL HDPE bottles.

Taro-Clarithromycin (Clarithromycin for Oral Suspension, USP) 250 mg/5 mL is supplied as a granular preparation in 105 mL HDPE bottles.

Taro-Clarithromycin (Clarithromycin for Oral Suspension, USP) is supplied as a white to off-white granular powder, forming white to off-white suspension on constitution with water. The bottles allow capacity for shaking. When reconstituted, the concentration of clarithromycin is 125 mg/5 mL and 250 mg/5mL respectively. The resulting suspension has a sweet taste and fruity flavor (tutti-fruity and peppermint).

Taro-Clarithromycin 125 mg/5 mL and 250 mg/5 mL oral suspensions contain less than 550 mg/mL of sucrose.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Clarithromycin should be administered with caution to any patient who has demonstrated some form of drug allergy, particularly to structurally related-drugs. If an allergic reaction to clarithromycin occurs, administration of the drug should be discontinued. Serious hypersensitivity reactions may require epinephrine, antihistamines, or corticosteroids. See **7 WARNINGS AND PRECAUTIONS, Immune, Hypersensitivity**.

Long-term use may, as with other antibiotics, result in colonization with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

Patients Infected with Human Immunodeficiency Virus

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

Myasthenia Gravis

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

Atypical Antipsychotics (quetiapine)

Due to inhibition of CYP3A by clarithromycin, co-administration of clarithromycin with quetiapine results in increased quetiapine concentrations. Serious and life-threatening quetiapine-related adverse reactions, including malignant neuroleptic syndrome, have been reported. Clarithromycin should not be used in combination with quetiapine unless clinically necessary. See **9 DRUG INTERACTIONS**. Monitoring and dose reductions may be required.

Oral Hypoglycemic Agents/Insulin

The concomitant use of clarithromycin and oral hypoglycaemic agents (such as sulphonylurias) and/or insulin can result in significant hypoglycaemia. Careful monitoring of glucose is recommended. See **9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4.**

Oral Anticoagulants

There is a risk of serious hemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving

clarithromycin and oral anticoagulants concurrently. See **9 DRUG INTERACTIONS, 9.4 Drug- Drug Interactions, Table 4.**

Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban and apixaban, particularly to patients at high risk of bleeding. See 9 DRUG INTERACTIONS**,** 9.4 Drug-Drug Interactions**.**

HMG-CoA Reductase Inhibitors

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated. See **CONTRAINDICATIONS**. Caution should be exercised when prescribing clarithromycin with statins. Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathy. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g., fluvastatin) can be considered. See **9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4.**

Triazolobenzodiazepines and Related Benzodiazepines

Caution is advised regarding the concomitant administration of clarithromycin with triazolobenzodiazepines (such as triazolam and alprazolam), or with other benzodiazepines (such as intravenous midazolam) due to the serious risk of central nervous system (CNS) effects (e.g., somnolence and confusion). **See 9 DRUG INTERACTIONS, Drug-Drug Interactions, Table 4.**

Concomitant administration with oral midazolam is contraindicated. See **2 2** CONTRAINDICATIONS.

Calcium Channel Blockers

Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) due to the risk of hypotension. See **9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4.**

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class. See **9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4.**

Other Drugs

Use of clarithromycin with other drugs may lead to drug-drug interactions, see **2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions.**

Carcinogenesis and Mutagenesis
See 16 NON-CLINICAL TOXICOLOGY

Cardiovascular

Cardiovascular Events

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including clarithromycin. See **8 ADVERSE REACTIONS**. Fatalities have been reported. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

As the following situations may lead to an increased risk for ventricular arrhythmias (including torsades de pointes), Clarithromycin should be used with caution in patients with coronary artery disease, cardiac insufficiency, conduction disturbances, clinically significant bradycardia (e.g., < 50 bpm), or when concomitantly taking with other medicinal products associated with QT prolongation, due to the risk for QT prolongation and torsades de pointes. See **9 DRUG INTERACTIONS**. Clarithromycin must not be given to patients with electrolyte disturbances such as hypomagnesaemia or hypokalemia. See 2 CONTRAINDICATIONS.

Clarithromycin is contraindicated in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia, including torsades de pointes. Clarithromycin is also contraindicated in patients with hypokalaemia due to the risk of QT prolongation and torsades de pointes. Concomitant administration of clarithromycin with astemizole, cisapride, domperidone, pimozide, terfenadine and saquinavir is also contraindicated. See **2 2** CONTRAINDICATIONS.

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Studies have identified risks of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.

Driving and Operating Machinery
There are no data on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

Endocrine and Metabolism

Taro-Clarithromycin (Clarithromycin for Oral Suspension, USP) contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

When prescribing to diabetic patients, the sucrose content should be taken into account. See **6 12 SPECIAL HANDLING INSTRUCTIONS**
There are no further special handling instructions for this product (see 11 STORAGE, STABILITY AND DISPOSAL).
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Phenylketonuric Patients
TARO-CLARITHROMYCIN contains aspartame. Aspartame contains phenylalanine which may pose safety risks in phenylketonuric (PKU) patients. See 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

Gastrointestinal

***Clostridium difficile*-Associated Disease**

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including clarithromycin. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile. Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases. See **8 ADVERSE REACTIONS**.

Hepatic/Biliary/Pancreatic

Caution is advised in patients with impaired hepatic function.

Clarithromycin is principally excreted by the liver and kidney. In patients with a combination of hepatic (mild to moderate) and renal impairments , decreased dosage of clarithromycin or prolonged dosing intervals might be appropriate. See **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**.

Clarithromycin is contraindicated in patients with severe hepatic failure in combination with renal impairment. See **CONTRAINDICATIONS**.

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 outcomes has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Immune

Hypersensitivity Reactions

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g., acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS)), clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Renal

Caution should be exercised when administering clarithromycin to advised in patients with moderate to severe renal impairment.

Clarithromycin is principally excreted by the liver and kidney. In patients with a combination of hepatic (mild to moderate) and renal impairments or in the presence of severe renal impairment, decreased dosage of clarithromycin or prolonged dosing intervals might be appropriate. See **4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment**.

Clarithromycin is contraindicated in patients with severe hepatic failure in combination with renal impairment. See **2 2** CONTRAINDICATIONS.

For the eradication of *H. pylori*, amoxicillin and clarithromycin should not be administered to patients with renal impairment since the appropriate dosage in this patient population has not yet been established.

Reproductive Health: Female and Male Potential
Fertility
See 16 NON-CLINICAL TOXICOLOGY; Reproductive and Developmental Toxicology. Please See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX. See 7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women.

Teratogenic Risk
Please See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX. See 7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women.

Sensitivity/Resistance

The development of resistance (11 out of 19 breakthrough isolates in 1 study) has been seen in HIV positive patients receiving clarithromycin for prophylaxis and treatment of MAC infection.

In view of the emerging resistance of *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Streptococcus pyogenes* to macrolides, it is important that susceptibility testing be performed when prescribing clarithromycin for community-acquired pneumonia and uncomplicated skin and skin structure infections.

To avoid failure of the eradication treatment with a potential for developing antimicrobial resistance and a risk of failure with subsequent therapy, patients should be instructed to follow closely the prescribed regimen.

Development of Drug-Resistant Bacteria

Prescribing TARO-CLARITHROMYCIN (clarithromycin for oral suspension) in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Antibiotic Resistance in Relation to Helicobacter pylori Eradication

Use of any antimicrobial therapy, such as clarithromycin, to treat *H. pylori* infection may select for drug-resistant organisms.

Triple Therapy with Omeprazole

Among the 113 triple therapy recipients with pretreatment *H. pylori* isolates susceptible to clarithromycin, 2/102 patients (2%) developed resistance after treatment with omeprazole, clarithromycin, and amoxicillin. Among patients who received triple therapy, 6/108 (5.6%) patients had pretreatment *H. pylori* isolates resistant to clarithromycin. Of these 6 patients, 3 (50%) had *H. pylori* eradicated at follow-up, and 3 (50%) remained positive after treatment. In 5/113 (4.4%) patients, no susceptibility data for clarithromycin pretreatment were available. Development of clarithromycin resistance should be considered as a possible risk especially when less efficient treatment regimens are used.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women. The benefits against risk, particularly during the first 3 months of pregnancy should be carefully weighed by a physician. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embryofoetal development cannot be excluded. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risks. Clarithromycin should not be used in pregnancy except where no alternative therapy is appropriate, particularly during the first 3 months of pregnancy. If pregnancy occurs while taking the drug, the patient should be apprised of the potential hazard to the fetus. See **3 Serious Warnings and Precautions Box**.

Four teratogenicity studies in rats (3 with oral doses and 1 with intravenous doses up to 160 mg/kg/day administered during the period of major organogenesis) and 2 in rabbits (at oral doses up to 125 mg/kg/day or intravenous doses of 30 mg/kg/day administered during gestation days 6 to 18) failed to demonstrate any teratogenicity from clarithromycin. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6 to 15. Plasma levels after 150 mg/kg/day were 2 times the human serum levels.

Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day 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 produced fetal growth retardation at plasma levels that were 2 times the human serum levels.

Embryonic loss has been seen in monkeys and rabbits. See **16 NON-CLINICAL TOXICOLOGY, Reproduction and Developmental Toxicology.**

7.1.2 Breast-feeding

The safety of clarithromycin for use during breast-feeding of infants has not been established. Clarithromycin is excreted in human milk in small amounts. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin.

Preweaned rats, exposed indirectly via consumption of milk from dams treated with 150 mg/kg/day for 3 weeks, were not adversely affected, despite data indicating higher drug levels in milk than in plasma.

7.1.3 Pediatrics

Pediatrics (6 months to 12 years of age): Use of clarithromycin for oral suspension, USP in children under 6 months has not been studied. In pneumonia, clarithromycin granules were not studied in children younger than 3 years.

The safety of clarithromycin has not been studied in MAC patients under the age of 20 months.

Neonatal and juvenile animals tolerated clarithromycin in a manner similar to adult animals. Young animals were slightly more intolerant to acute overdosage and to subtle reductions in erythrocytes, platelets and leukocytes, but were less sensitive to toxicity in the liver, kidney, thymus and genitalia.

Increased valproate and phenobarbital concentrations and extreme sedation were noted in a 3-year old patient coincident with clarithromycin therapy. Cause and effect relationship cannot be established. However, monitoring of valproate and phenobarbital concentrations may be considered.

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Drug Reaction Overview

In pediatric patients taking clarithromycin for oral suspension, USP, the most frequently reported events were diarrhea, vomiting, abdominal pain, dyspepsia, taste perversion and infection.

8.2 Clinical Trial Adverse Drug Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Clarithromycin for Oral Suspension:

The safety profile of clarithromycin for oral suspension is similar to that of the 250 mg tablet in adult patients.

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

Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis and Stevens-Johnson Syndrome/toxic epidermal necrolysis have occurred with orally administered clarithromycin.

There have been rare reports of pancreatitis and convulsions.

Of the 1829 patients who received clarithromycin for oral suspension, 571 (31%) reported at least one adverse event. The adverse events reported are summarized in **Table** .

Table 2
Adverse Events Reported in Pediatric Clinical Trials

System Organ Class	**Number (%) of Patients N = 1829**
Infections and infestations	172 (9%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (< 1%)
Blood and the lymphatic system disorders	14 (< 1%)
Metabolism and nutrition disorders	9 (< 1%)
Psychiatric disorders	12 (0.7%)
Nervous system disorders	41 (2%)
Eye disorders	22 (1%)
Ear and labyrinth disorders	25 (1%)
Vascular disorders	2 (< 1%)
Respiratory, thoracic and mediastinal disorders	61 (3%)
Gastrointestinal disorders	355 (19%)
Skin and subcutaneous disorders	66 (4%)
Musculoskeletal and connective tissue disorders	2 (< 1%)
Renal and urinary disorders	5 (< 1%)
Reproductive system and breast disorders	2 (< 1%)
General disorders and administration site conditions	56 (3%)
Investigations	29 (2%)
Injury, poisoning and procedural complications	19 (1%)
TOTAL*	571 (31%)

*Patients with more than one event within a system organ class are only counted once in the total for that system organ class. Patients with events in more than one system organ class are counted only once in the overall total.

The majority of the patients reported adverse event in the Gastrointestinal disorders SOC (19%), and the Infections and infestations SOC (9%).

The events occurring most frequently in the Gastrointestinal disorder SOC were diarrhea (7%), vomiting (7%), abdominal pain (3%), dyspepsia (3%) and nausea (1%).

Other adverse events included infection (3%), rhinitis (2.2%), rash (2.2%), increased cough (2.1%), fever (2.2%), headache (1.6%), conjunctivitis (1.1%), dysgeusia (3%) and transient elevation of AST (0.9%).

The majority of adverse events were considered by the investigators to have either mild or moderate severity. Three hundred and seventy-five of 1829 patients (21%) had mild adverse events, 175/1829 patients (10%) had moderate adverse events and 20/1829 patients (1%) had severe adverse events.

In the 2 U.S. acute otitis media studies of clarithromycin *versus* antimicrobial/beta-lactamase inhibitor, the incidence of adverse events in all patients treated, primarily diarrhea (15% *vs*. 38%) and diaper rash (3% *vs*. 11%) in young children, was clinically or statistically lower in the clarithromycin arm *versus* the control arm.

In another U.S. otitis media study of clarithromycin *versus* cephalosporin, the incidence of adverse events in all patients treated, primarily diarrhea and vomiting, did not differ clinically or statistically for the 2 agents.

8.3 Less Common Clinical Trial Adverse Reactions

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Clarithromycin for Oral Suspension:

The following adverse drug reactions are applicable to all indications approved for this formulation.

Blood and Lymphatic System Disorders:	thrombocythemia
General Disorders and Administration Site Conditions:	pyrexia
Infections and Infestations:	Infection
Musculoskeletal and Connective Tissue Disorders:	muscle spasms
Psychiatric Disorders:	nervousness
Skin and Subcutaneous Tissue Disorders:	rash maculo-papular

Other adverse reactions have been observed in different patient populations and during post-marketing surveillance. See **8 ADVERSE REACTIONS**, **Clinical Trial Adverse Drug Reactions**, **Table .**

8.5 Post-Market Adverse Drug Reactions

The following list of adverse events is a compilation of adverse reactions from Post-marketing Surveillance and Post-marketing Clinical Studies for all clarithromycin formulations.

Table 3
Post-Market Adverse Drug Reactions

System Organ Class	Adverse Event
Blood and lymphatic system disorders	Leukopenia
	Thrombocytopenia
	Agranulocytosis
Cardiac disorders[1]	Atrial fibrillation
	Cardiac arrest
	Extrasystoles
	Electrocardiogram QT prolonged
	Ventricular fibrillation
	Ventricular tachycardia
	Torsades de pointes
	Palpitations
Ear and labyrinth disorders	Tinnitus
	Hearing loss[2]
	Deafness
	Hearing impaired
	Vertigo
Gastrointestinal disorders	Abdominal pain
	Constipation
	Dyspepsia
	Dry mouth
	Eructation
	Esophagitis
	Flatulence
	Vomiting
	Glossitis
	Gastritis
	Stomatitis
	Tongue discolouration
	Tooth discolouration
	Pancreatitis
General disorders and administration site conditions	Asthenia
Hepatobiliary disorders	Hepatitis
	Hepatitis cholestatic
	Hepatic failure[3]
	Jaundice (cholestatic and hepatocellular)
Immune system disorders	Angioedema
	Anaphylaxis
	Anaphylactic reaction
	Anaphylactoid reaction
	Hypersensitivity
	Myasthenia gravis
Infections and infestations	Candidiasis
	Cellulitis
	Pseudomembranous colitis
	Vaginal infection

Table 3 Post-Market Adverse Drug Reactions	
System Organ Class	**Adverse Event**
Investigations	Albumin globulin ratio abnormal
	Alanine aminotransferase increased
	Aspartate aminotransferase increased
	Liver function test abnormal
	Liver enzymes increased
	Blood creatinine increased
	Blood urea increased
	International normalized ratio (INR) increased[4]
	Prothrombin time prolonged[4]
	Urine color abnormal[5]
Metabolism and nutrition disorders	Anorexia
	Decreased appetite
Musculoskeletal and connective tissue disorders	Myalgia
	Myopathy
	Rhabdomyolysis[6]
	Musculoskeletal stiffness
Nervous system disorders	Dizziness
	Tremor
	Alteration of sense of smell
	Convulsions
	Ageusia
	Anosmia
	Loss of consciousness
	Parosmia
	Somnolence
	Dysgeusia
	Dyskinesia
	Headache
	Paraesthesia
Psychiatric disorders	Anxiety
	Insomnia
	Abnormal dreams
	Confusion
	Disorientation
	Hallucination
	Psychosis
	Depersonalization
	Depression
	Mania
Renal and urinary disorders	Interstitial nephritis
	Renal failure
Respiratory, thoracic and mediastinal disorders	Asthma
	Pulmonary embolism
Skin and subcutaneous tissue disorders	Acne
	Dermatitis bullous
	Drug rash with eosinophilia and systemic symptoms (DRESS)
	Henoch-Schonlein purpura
	Pruritus

Table 3 Post-Market Adverse Drug Reactions	
System Organ Class	**Adverse Event**
	Hyperhidrosis
	Urticaria
	Rash
	Stevens Johnson syndrome
	Toxic epidermal necrosis
Vascular disorders	Hemorrhage[4]
	Vasodilation

1 As with other macrolides, QT prolongation, ventricular tachycardia, and torsades de pointes have been reported with clarithromycin.
2 There have been reports of hearing loss with clarithromycin which is usually reversible upon withdrawal of therapy.
3 Hepatic dysfunction may be severe and is usually reversible. Hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.
4 When clarithromycin is co-administered with warfarin.
5 Symptom of hepatic failure.
6 In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with other drugs known to be associated with rhabdomyolysis (such as statins, fibrates, colchicine or allopurinol).

Colchicine

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

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concomitant administration of clarithromycin with astemizole, cisapride, domperidone, colchicine, pimozide, terfenadine, lovastatin, simvastatin, ergot alkaloids (e.g., ergotamine, dihydroergotamine) is contraindicated. See **2 CONTRAINDICATIONS** and **9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions**.
- Clarithromycin is an inhibitor of the cytochrome P450 3A isoform subfamily (CYP3A) and the P-glycoprotein transporter (P-gp). The concomitant administration of clarithromycin and drugs metabolized by CYP3A and/or transported by P-gp may lead to an increase in the plasma concentrations of the co-administered drug which could result in clinically significant safety concerns.

9.2 Drug Interactions Overview

Many categories of drugs are metabolized by CYP3A and/or transported by P-gp located in the liver and in the intestine. Some drugs may inhibit or induce the activities of CYP3A and/or P-gp. Administration of such inhibitors or inducers may impact upon the metabolism. In some cases serum concentrations may be increased and in others decreased. Care must therefore be exercised when co-administering such drugs.

Effects of Clarithromycin on Other Drugs

Clarithromycin is an inhibitor of CYP3A and P-gp. This inhibition may lead to increased or prolonged serum levels of those drugs also metabolized by CYP3A or transported by P-gp when co-administered with clarithromycin. For such drugs the monitoring of their serum concentrations may be necessary.

Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A and/or P-gp substrates, especially if the CYP3A/P-gp substrate has a narrow safety margin (e.g., carbamazepine) and/or the substrate is extensively metabolized by CYP3A or transported by P-gp. Dosage adjustments may be considered, and when possible, serum concentrations of these drugs should be monitored closely in patients concurrently receiving clarithromycin.

The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, domperidone, ergot alkaloids, ibrutinib, lomitapide, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, triazolam and vinblastine, but this list is not comprehensive. See 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions.
Direct acting oral anticoagulants (DOACs): The DOAC dabigatran is a substrate for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolised via CYP3A4 and are also substrates for P-gp. Caution should be exercised when clarithromycin is co-administered with these agents particularly to patients at high risk of bleeding. See 7 WARNINGS AND PRECAUTIONS, General.

With certain drugs, co-administration of clarithromycin is contraindicated or should be avoided (see **Table 3**).

Effects of Other Drugs on Clarithromycin

Clarithromycin is a substrate of CYP3A. Co-administration of strong inducers of the cytochrome P450 metabolism system may accelerate the metabolism of clarithromycin and thus lower exposure to clarithromycin while increasing exposure to its metabolite 14-OH-clarithromycin which could impair the intended therapeutic effect. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the

CYP3A4 inducer administered). Co-administration of potent CYP3A inhibitors may lead to increased exposure to clarithromycin and decreased exposure to its metabolite 14-OH-clarithromycin. Clarithromycin dosage adjustment or consideration of alternative treatments may be required.

Bi-Directional Drug Interactions

Bi-directional drug interactions are complex and may occur if both of the interacting drugs are substrates and inhibitors/inducers of CYP3A.

Additional Mechanisms

Interactions with clarithromycin have been reported with drugs metabolized by cytochrome P450 isoforms other than CYP3A system. Additional mechanisms, such as effects upon absorption, may also be responsible for interaction between drugs, including zidovudine and clarithromycin.

9.3 Drug-Behavioural Interactions

This information is not available for this drug product.

9.4 Drug-Drug Interactions

Some of the drug-drug interactions which have been reported between clarithromycin-macrolides and other drugs or drug categories are listed in **Table** .

The drugs listed in this table are based on either drug interactions case reports or studies or potential interactions due to the expected magnitude and seriousness of the interaction. (i.e., those identified as contraindicated).

Table 4 Established or Potential Drug-Drug Interactions with Clarithromycin			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
Astemizole* / Terfenadine	CT	terfenadine-acid metabolite concentrations increase ↑ QT interval	Macrolides have been reported to alter the metabolism of terfenadine resulting in increased serum levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsade de pointes. See **2 CONTRAINDICATIONS**. In a study involving 14 healthy volunteers, the concomitant administration of clarithromycin tablets (film-coated) and terfenadine resulted in a 2- to 3-fold increase in the serum levels of the acid metabolite of terfenadine, MDL 16, 455, and in prolongation of the QT interval. Similar effects have been observed with concomitant administration of astemizole and other macrolides.
Atazanavir	CT	↑ clarithromycin levels ↑ atazanavir AUC	Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH-clarithromycin, with a 28% increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance < 30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.
Atypical Antipsychotics (e.g. quetiapine)		Potential ↑ in concentrations of quetiapine and other atypical antipsychotics	Clarithromycin should not be used in combination with quetiapine unless clinically necessary. Due to CYP3A inhibition by clarithromycin, concentrations of quetiapine are expected to increase, which can result in serious and/or life-threatening adverse reactions, including malignant neuroleptic syndrome. For other atypical antipsychotic drugs (aripiprazole and risperidone) metabolized by CYP3A4, it is also recommended that concomitant administration with clarithromycin be avoided due to potential pharmacokinetic interactions.
Calcium Channel Blockers (e.g., verapamil, amlodipine, diltiazem)	C	Potential ↑ in verapamil concentrations	Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class.

Table 4 Established or Potential Drug-Drug Interactions with Clarithromycin			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
Carbamazepine	C	↑ levels of carbamazepine	Clarithromycin administration in patients receiving carbamazepine has been reported to cause increased levels of carbamazepine. Blood level monitoring of carbamazepine should be considered.
Cisapride* / Pimozide	C	↑ levels of cisapride ↑ levels of pimozide	Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsade de pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly. See **2 CONTRAINDICATIONS**.
Colchicine	C	Potential colchicine toxicity	Colchicine is a substrate for both CYP3A and the efflux transporter, P-gp. Clarithromycin and other macrolides are known to inhibit CYP3A and P-gp. When clarithromycin and colchicine are administered together, inhibition of P-gp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. This risk may be further increased with concomitant medications metabolized by P-glycoprotein or strong CYP3A inhibitors. Concomitant use of clarithromycin and colchicine is contraindicated. . See **2 CONTRAINDICATIONS**.
Cyclosporine	C	↑ levels of cyclosporine	There have been reports of elevated cyclosporine serum concentrations when clarithromycin and cyclosporine are used concurrently. Cyclosporine levels should be monitored and the dosage should be adjusted as necessary. Patients should also be monitored for increased cyclosporine toxicity.
Didanosine	CT	No change in didanosine pharmacokinetics in HIV-infected patients (n = 12)	Simultaneous administration of clarithromycin tablets (film-coated) and didanosine to 12 HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.
Digoxin	C	↑ levels of digoxin	Digoxin is thought to be a substrate for the efflux transporter, P-gp. Clarithromycin is known to inhibit P-gp. When clarithromycin and digoxin are administered together, inhibition of P-gp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations have been reported in patients receiving clarithromycin tablets (film-coated) and digoxin concomitantly. In post-marketing surveillance some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin levels should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.
Disopyramide / Quinidine	C	↑ levels of disopyramide, resulting in ventricular fibrillation & QT prolongation (rarely reported)	Increased disopyramide plasma levels, resulting in ventricular fibrillation and QT prolongation, coincident with the co-administration of disopyramide and clarithromycin have rarely been reported.

Table 4 Established or Potential Drug-Drug Interactions with Clarithromycin			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
		Torsades de pointes	There have been post-marketed reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during co-administration of clarithromycin with these drugs. Serum levels of these medications should be monitored during clarithromycin therapy. 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.
Domperidone	C, P	↑ levels of domperidone, resulting in QT prolongation and cardiac arrhythmias	Elevated domperidone levels have been reported in patients receiving a potent CYP3A4 inhibitor and domperidone concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Hence, co-administration of domperidone with QT-prolonging medicines and/or potent CYP3A4 inhibitors such as clarithromycin is contraindicated. See **2 CONTRAINDICATIONS**.
Ergot alkaloids Ergotamine / Dihydroergotamine	C	Potential ischemic reactions Potential ergot toxicity	Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by severe peripheral vasospasm, dysesthesia, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and ergot alkaloids is contraindicated. See **2 CONTRAINDICATIONS**
Etravirine	CT	↓ clarithromycin ↑ 14-OH-clarithromycin	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.
Fluconazole	CT	↑ clarithromycin C_{min} & AUC	Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state clarithromycin C_{min} and AUC of 33% and 18%, respectively. Steady-state concentrations of 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.
HMG-CoA Reductase Inhibitors Lovastatin / Simvastatin	C	Rhabdomyolysis (rarely reported)	Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see **2 CONTRAINDICATIONS**) as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with

Table 4 Established or Potential Drug-Drug Interactions with Clarithromycin			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
Atorvastatin Rosuvastatin	C		clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment. See WARNINGS AND PRECAUTIONS, HMG-CoA Reductase Inhibitors. Rare reports of rhabdomyolysis have also been reported in patients taking atorvastatin or rosuvastatin concomitantly with clarithromycin. Concurrent use of atorvastatin and clarithromycin may result in increased atorvastatin exposure. Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g., fluvastatin) can be considered. Patients should be monitored for signs and symptoms of myopathy.
Itraconazole	CT, P	↑ levels of clarithromycin ↑ levels of itraconazole	Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bi-directional drug interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.
Lansoprazole/ Omeprazole	CT	Mild change of lansoprazole and 14-OH-clarithromycin concentrations ↑ omeprazole C_{max} & AUC_{0-24} ↑ levels of clarithromycin	One study demonstrated that concomitant administration of clarithromycin and lansoprazole resulted in mild changes of serum concentrations of lansoprazole and 14-OH-clarithromycin. However, no dosage adjustment is considered necessary based on these data. Clarithromycin 500 mg three times daily was given in combination with omeprazole 40 mg once daily to healthy subjects. The steady-state plasma concentrations of omeprazole were increased (i.e., C_{max}, AUC_{0-24}, and $t_{1/2}$ increased by 30%, 89%, and 34%, respectively), by concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when co-administered with clarithromycin. To a lesser extent, omeprazole administration increases the serum concentrations of clarithromycin. Omeprazole administration also increases tissue and mucus concentrations of clarithromycin.

Table 4 Established or Potential Drug-Drug Interactions with Clarithromycin			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
Oral Anticoagulants Warfarin / Acenocoumarol	C	↑ anticoagulant effect	There have been reports of increased anticoagulant effect when clarithromycin and oral anticoagulants are used concurrently. Anticoagulant parameters should be closely monitored. Adjustment of the anticoagulant dose may be necessary. Clarithromycin has also been reported to increase the anticoagulant effect of acenocoumarol. There is a risk of serious hemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently. See WARNINGS AND PRECAUTIONS, Use with Other Drugs, Oral Anticoagulants.
Oral Hypoglycemic Agents (e.g.,Insulin)	C P	Hypoglycemia	The concomitant use of clarithromycin and oral hypoglycaemic agents and/or insulin can result in significant hypoglycaemia. With certain hypoglycaemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia when used concomitantly. Careful monitoring of glucose is recommended.
Phosphodiesterase Inhibitors (e.g., sildenafil, tadalafil, vardenafil)	P	↑ phosphodiesterase inhibitor exposure	Sildenafil, tadalafil, and vardenafil are metabolized, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these drugs are co-administered with clarithromycin.
Rifabutin	C	↓ clarithromycin ↑ rifabutin	Clarithromycin has been reported to increase serum and tissue concentration of rifabutin and thus may increase the risk of toxicity. Clarithromycin levels decrease when co-administered with rifabutin. Concomitant administration of clarithromycin and rifabutin in the treatment of *Mycobacterial Avium* complex infections resulted in rifabutin-associated uveitis. A case control study in AIDS patients showed that concomitant administration of rifabutin and clarithromycin resulted in an approximately 50% reduction in serum clarithromycin concentration, approximately 77% increase in the area under the plasma concentration-time curve of rifabutin, and a 236% increase in the area under the plasma concentration-time curve of rifabutin's active metabolite. The increase in rifabutin and/or its metabolite contributed to the development of uveitis (the incidence of uveitis was 14% in patients weighing >65 kg, 45%in patients between 55 and 65 kg, and 64%in patients <55 kg).

Table 4 Established or Potential Drug-Drug Interactions with Clarithromycin			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
Ritonavir / Indinavir	CT	↑ clarithromycin C_{max}, C_{min}, & AUC ↑ indinavir AUC ↑ clarithromycin AUC	A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every 8 hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin C_{max} increased by 31%, C_{min} increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-[R]-hydroxy-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with creatinine clearance 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with creatinine clearance < 30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1g/day should not be co-administered with ritonavir. Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir. One study demonstrated that the concomitant administration of clarithromycin and indinavir resulted in a metabolic interaction; the clarithromycin AUC increased by 53% and the indinavir AUC was increased by 20%, but the individual variation was large. No dose adjustment is necessary with normal renal function.
Saquinavir	CT	↑ saquinavir AUC and C_{max} ↑ clarithromycin AUC	Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) for 7 days to 12 healthy volunteers resulted in steady-state AUC and C_{max} values of saquinavir which were 177% (108-269%) and 187% (105-300%) higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} values were approximately 40% higher than those seen with clarithromycin alone. [Clarithromycin AUC ↑ 45% (17-81%) and C_{max} ↑ 39% (10-76%); 14-OH clarithromycin metabolite AUC ↓ 24% (5-40%) and C_{max} ↓ 34% (14-50%)]. QTc prolongation has been reported in patients taking saquinavir along with ritonavir and also in patients taking clarithromycin. Concurrent administration of saquinavir and clarithromycin is contraindicated (see **2 2** CONTRAINDICATIONS).
Tacrolimus	P	Potential ↑ in tacrolimus concentrations	Concomitant administration of tacrolimus and clarithromycin may result in increased plasma levels of tacrolimus and increased risk of toxicity.

Table 4 Established or Potential Drug-Drug Interactions with Clarithromycin			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
Theophylline	P	Potential ↑ in theophylline concentrations	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.
Tolterodine	P	↑ serum tolterodine concentrations	The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (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. A reduction of tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metabolizer population.
Triazolobenzodiaz-epines (e.g., triazolam, alprazolam) Other related benzodiazepines (e.g., midazolam)	CT, C, P	↑ midazolam AUC	When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. See **2 2** CONTRAINDICATIONS. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment of midazolam. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely. 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.
Zidovudine	C	Potential ↓ in zidovudine concentrations	Simultaneous oral administration of clarithromycin tablets (film-coated) and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, and therefore, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine. This interaction does not appear to occur in pediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. Similar interaction studies have not been conducted with clarithromycin extended-release (ER) and zidovudine.

Table 4 Established or Potential Drug-Drug Interactions with Clarithromycin			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
Other drugs metabolized by CYP3A (e.g., alfentanil, bromocriptine, cilostazol, methylprednisolone, vinblastine)	C, P	Potential increase in serum concentration	Interactions with erythromycin and/or clarithromycin have been reported with a number of other drugs metabolized by CYP3A, such as alfentanil, bromocriptine, cilostazol, methylprednisolone, or vinblastine. Serum concentrations of drugs metabolized by CYP3A should be monitored closely in patients concurrently receiving erythromycin or clarithromycin.
Other drugs metabolized by cytochrome P450 isoforms other than CYP3A (e.g., hexobarbital, phenytoin, and valproate)	C, P	Potential change in serum concentration	Interactions with erythromycin and/or clarithromycin have been reported with drugs metabolized by other cytochrome P450 isoforms (i.e., not CYP3A), such as hexobarbital, phenytoin, and valproate. Serum concentrations of these drugs should be monitored closely in patients concurrently receiving erythromycin or clarithromycin.
Other drug inducers of the cytochrome P450 system (e.g, efavirenz, nevirapine, rifampin, rifabutin, rifampicin, phenobarbital, rifapentine)	CT, P	↓ levels of clarithromycin	Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampin, rifabutin, rifampicin, phenobarbital and rifapentine* may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14-OH- clarithromycin, a metabolite that is also microbiologically active. 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.
Legend: C = Case Study; CT = Clinical Trial; P = Potential Interactions with other drugs have not been established. *not marketed in Canada.			

Combination Therapy with Omeprazole and/or Amoxicillin

For more information on drug interactions for omeprazole and amoxicillin, refer to their respective Product Monographs, under **9 DRUG INTERACTIONS**.

9.5 Drug-Food Interactions

Taro-Clarithromycin (Clarithromycin for Oral Suspension, USP) may be given with or without meals.

9.6 Drug-Herb Interactions

St. John's Wort (*Hypericum perforatum*) is an inducer of CYP3A and may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy.

9.7 Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

General

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible bacteria and suppressing protein synthesis.

10.2 Pharmacodynamics

Eradication of Helicobacter pylori

H. pylori is now established as a major etiological factor in duodenal ulcer disease. The presence of *H. pylori* may damage the mucosal integrity due to the production of enzymes (catalase, lipases, phospholipases, proteases, and urease), adhesins and toxins; the generated inflammatory response contributes to mucosal damage.

The concomitant administration of an antimicrobial(s) such as clarithromycin and an antisecretory agent, improves the eradication of *H. pylori* as compared to individual drug administration. The higher pH resulting from antisecretory treatment optimizes the environment for the pharmacologic action of the antimicrobial agent(s) against *H. pylori*.

10.3 Pharmacokinetics

A summary of clarithromycin pharmacokinetic parameters in adult volunteers following the administration of clarithromycin for oral suspension is provided in **Table 1**. See 10 CLINICAL PHARMACOLOGY, Detailed Pharmacology.

Table 1
Clarithromycin Pharmacokinetic Parameters in Adult Subjects following the Administration of Clarithromycin for Oral Suspension

250 mg/10 mL	**C_{max} (mg/L)**	**T_{max} (hr)**	**$t_{½}$ (hr)**	**$AUC_{0-\infty}$ (mg●hr/L)**
Mean (fasting conditions)	1.24	3.3	3.7	7.2
Mean (fed conditions)	0.95	5.3	3.7	6.5

A summary of clarithromycin pharmacokinetic parameters in pediatric patients following the administration of clarithromycin for oral suspension is provided in **Table 2**. See **DETAILED PHARMACOLOGY, Pharmacokinetics**.

Table 2
Clarithromycin Pharmacokinetic Parameters in Pediatric Patients following the Administration of Clarithromycin for Oral Suspension

	C_{max} (mg/L)	**t_{max}** (hr)	**AUC_{0-t}** (mg●hr/L)
Single Dose (125 mg/5 mL)			
Mean (fasting conditions)	3.59	3.1	10
Mean (fed conditions)	4.58	2.8	14.2
Multiple Doses (7.5 mg/kg b.i.d.)			
Mean (fasting conditions)	4.6	2.8	15.7
Legend: b.i.d. = twice daily			

Absorption

Adult Volunteers

Single and multiple dose adult volunteer studies showed that the suspension formulation was not significantly different from the tablet formulation in terms of C_{max} of clarithromycin and AUC, although the onset and/or rate of absorption of the suspension formulation was slower than that of the tablet. As with the tablet formulation, steady-state is achieved by the fifth dose of a 12 hour multiple-dose suspension regimen.

Children

In children taking 15 to 30 mg/kg/day in two divided doses, steady-state clarithromycin C_{max} values generally ranged from 8 to 20 mcg/mL. C_{max} values as high as 23 mcg/mL have been observed in HIV-infected pediatric patients taking 30 mg/kg/day in two divided doses. In children requiring antibiotic therapy, administration of 7.5 mg/kg q12h doses every 12 hours of clarithromycin as the suspension generally resulted in steady-state peak plasma concentrations of 3 to 7 mcg/mL for clarithromycin, and 1 to 2 mcg/mL for 14-OH-clarithromycin. In HIV-infected children taking 15 mg/kg every 12 hours, steady-state clarithromycin peak concentrations generally ranged from 6 to 15 mcg/mL. A single and multiple dose study conducted in pediatric patients showed that food leads to a slight delay in the onset of absorption, but does not affect the overall bioavailability of clarithromycin.

Clarithromycin and its 14-OH metabolite penetrate into middle ear effusion (MEE) of patients with secretory otitis media.

For adult patients, the bioavailability of 10 mL of the 125 mg/5mL suspension is similar to a 250 mg tablet.

Single dose adult volunteer studies show that the reformulated (125 mg/5 mL and 250 mg/5 mL) and the current (125 mg/5 mL) clarithromycin for oral suspension have comparable bioavailability under fasting and non-fasting conditions.

Distribution

Clarithromycin distributes readily into body tissues and fluids, and provides tissue concentrations that are higher than serum concentrations. Examples from tissue and serum concentrations are presented in **Table 7**.

Table 3
Representative Clarithromycin Tissue and Serum Concentrations Following the Administration of 250 mg b.i.d of Clarithromycin Film-Coated Tablets

	Concentrations	
Tissue Type	**Tissue (mcg/g)**	**Serum (mg/L)**
Tonsil	1.6	0.8
Lung	8.8	1.7
Leukocytes*	9.2	1.0

* *in vitro* data.
Legend: b.i.d. = twice daily

Metabolism

Clarithromycin is principally excreted by the liver and kidney. The major metabolite found in urine is 14-OH-clarithromycin.

Elimination

At 250 mg twice daily, approximately 20% of an orally administered dose of clarithromycin film-coated tablet is excreted in the urine as the unchanged parent drug. The urinary excretion of unchanged clarithromycin is somewhat greater (approximately 30%) with 500 mg twice daily dosing. 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 twice daily dosing at either 250 mg or 500 mg. Most of the remainder of the dose is eliminated in the feces, primarily via the bile. About 5 to 10% of the parent drug is recovered from the feces. Fecal metabolites are largely products of N-demethylation, 14-hydroxylation or both.

Special Populations and Conditions

Pediatrics

See 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Absorption.

Geriatrics

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

Hepatic Insufficiency

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 subjects with impaired hepatic function when compared to healthy subjects. See **7 3 SERIOUS WARNINGS** AND PRECAUTIONS**, Hepatic/Biliary/Pancreatic** and **4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**.

Renal Insufficiency

The elimination of clarithromycin was impaired in patients with impaired renal function. The daily dose of clarithromycin should be limited to 500 mg in patients with severe renal impairment (creatinine clearance < 30 mL/min). See **7 3 SERIOUS WARNINGS** AND PRECAUTIONS**, Renal** and **4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment**.

DETAILED PHARMACOLOGY

General

Helicobacter pylori

The presence of *H. pylori* may damage the mucosal integrity and defenses so that exposure to acid/pepsin, even in normal concentrations, produces ulceration.

H. pylori displays potent urease activity which may produce an alkaline environment around the organism. Excess ammonia produced by urea hydrolysis is toxic to mucosal cells and may lead to parietal cell failure and/or to a disturbance of the normal negative feedback of acid to the antral G-cells which secrete gastrin. In addition, *H. pylori* produces catalases, lipases, phospholipases, proteases, adhesins and toxins. These enzymes may further degrade the mucous layer and damage the epithelial cell membrane. Also, the presence of *H. pylori* stimulates an active inflammatory response which contributes to mucosal damage.

Gustavson *et al.* (1995) showed that concentrations of 39.3, 23.1 and 25.2 mcg/g clarithromycin were achieved in the gastric mucosa 2, 4, and 6 hours respectively after administering 500 mg clarithromycin three times daily and that corresponding concentrations of the 14-OH metabolite were 3.2, 1.1, and 4.1 mcg/g respectively. Similar results were obtained whether or not clarithromycin was given alone or together with 40 mg omeprazole once daily (Logan *et al*., 1995). Although the activity of the 14-OH metabolite is about half of the parent drug and its concentrations are lower, it may still contribute antibacterial activity.

Pharmacokinetics

Pharmacokinetics for clarithromycin and 14-OH-clarithromycin metabolite following the oral administration of a single dose or multiple doses of clarithromycin are outlined below.

Clarithromycin and Omeprazole

A pharmacokinetic study was conducted with clarithromycin 500 mg three times daily and omeprazole 40 mg once daily. When clarithromycin was given alone at 500 mg every 8 hours, the mean steady-state C_{max} value was approximately 31% higher and the mean C_{min} value was approximately 119% higher than when clarithromycin is compared with a previous study at 500 mg every 12 hours. The mean AUC_{0-24} for clarithromycin was 65% greater when 500 mg clarithromycin was given every 8 hours rather than every 12 hours. Neither T_{max} nor half-life values appeared substantially different between the every-8-hour and every-12-hour regimens.

When clarithromycin was administered with omeprazole, increases in omeprazole half-life and AUC_{0-24} were observed. For all subjects combined, the mean omeprazole AUC_{0-24} was 89% greater and the harmonic mean for omeprazole $t_{½}$ was 34% greater when omeprazole was administered with clarithromycin than when omeprazole was administered alone. When clarithromycin was administered with omeprazole, the steady-state C_{max}, C_{min}, and AUC_{0-8} of clarithromycin were increased by 10%, 27%, and 15%, respectively over values achieved when clarithromycin was administered with placebo.

At steady-state, clarithromycin gastric mucus concentrations 6 hours post dosing were approximately 25-fold higher in the clarithromycin/omeprazole group compared with the clarithromycin alone group. Six hours post-dosing, mean clarithromycin gastric tissue concentrations were approximately 2-fold higher when clarithromycin was given with omeprazole than when clarithromycin was given with placebo.

Clarithromycin distributes readily into body tissues and fluids, and provides tissue concentrations that are higher than serum concentrations. Examples from tissue and serum concentrations are presented in Error! Reference source not found..

Table 4
Representative Clarithromycin Tissue and Serum Concentrations

Tissue Type	**Concentrations (after 250 mg b.i.d.)**	
	Tissue (mcg/g)	**Serum (mcg/mL)**
Tonsil	1.6	0.8
Lung	8.8	1.7
Leukocytes*	9.2	1.0

* *in vitro* data.
Legend: b.i.d.= twice daily

Clarithromycin for Oral Suspension, USP

Adults

Plasma concentrations of clarithromycin and 14-OH-clarithromycin were studied in 17 healthy male adult volunteers following the administration of clarithromycin granules for suspension. A single phase dose was followed by the multiple dose phase. During the single dose phase, an oral 250 mg (10 mL) dose of clarithromycin granules for suspension was administered. Doses were administered in a fasting state (2 hours before breakfast after an overnight fast and 2 hours after dinner). Mean plasma concentrations of clarithromycin and 14-OH-clarithromycin are illustrated in Error! Reference source not found..

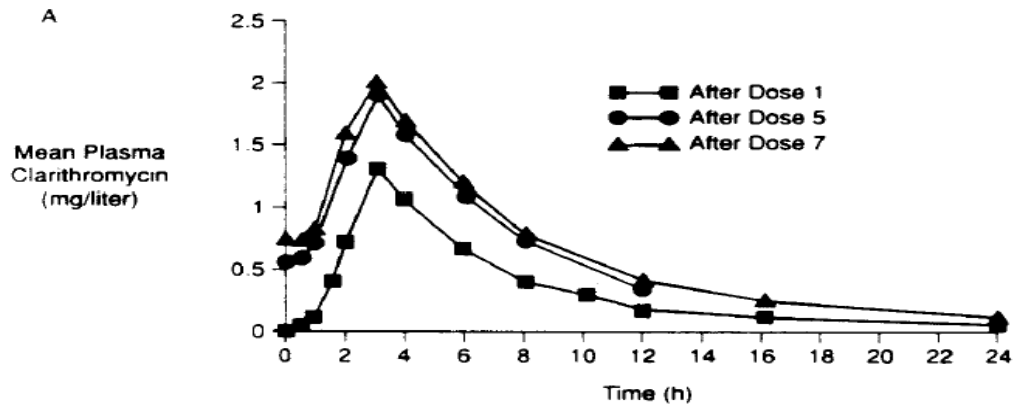


Figure 1:Mean Plasma Clarithromycin (A) and 14-OH-Clarithromycin (B) Concentration of Single and Multiple (Every 12-hours) Dose Administration(s) of 250 mg of Clarithromycin

A summary of pharmacokinetic parameters is presented in Error! Reference source not found.. After a single- and multiple-dose administration of clarithromycin as a suspension formulation, times to attain peak plasma clarithromycin and 14-OH-clarithromycin concentrations were prolonged, as evidenced by mean T_{max} values ranging from 2.8 to 3.2 and 2.9 to 3.4 hours, respectively. Steady-state was achieved by Dose 5.

Table 5
Clarithromycin and 14-OH-Clarithromycin Pharmacokinetic Parameters

Parameters	Single Dose Mean ± SD	5th Dose Mean ± SD	7th Dose Mean ± SD	Comparison[1]	
				1 vs 5	5 vs 7
Clarithromycin					
C_{max} (mcg/mL)	1.34 ± 0.37	1.98 ± 0.55	2.15 ± 0.62	*	NS
T_{max} (hr)	3.2 ± 1.1	2.8 ± 0.6	3.1 ± 0.9	--	--
C_{min} (mcg/mL)	0.17 ± 0.10	0.32 ± 0.22	0.39 ± 0.25	*	*
AUC[2] (mcg•hr/mL)	7.80 ± 2.87	11.5 ± 4.6	12.7 ± 4.8	*	NS
$t_{½}$[3] (hr)	3.6	3.2	3.5	--	--
f_u (% of dose)	--	36.9 ± 11.1	40.0 ± 14.0	--	NS
14-OH-Clarithromycin					
C_{max} (mcg/mL)	0.46 ± 0.16	0.67 ± 0.15	0.72 ± 0.16	*	NS
T_{max} (hr)	3.4 ± 1.2	2.9 ± 1.0	3.0 ± 1.0	--	--
C_{min} (mcg/mL)	0.14 ± 0.04	0.23 ± 0.07	0.27 ± 0.07	*	*
AUC[2] (mcg•hr/mL)	4.87 ± 1.24	5.33 ± 1.20	5.85 ± 1.17	*	*
$t_{½}$[3] (hr)	7.2	4.9	6.4	--	--
f_u (% of dose)	--	17.1 ± 3.1	18.4 ± 5.0	--	NS

[1] Comparison was based on t-statistics within repeated measures ANOVA framework. Statistical significance is shown as NS if $p > 0.05$ and * if $p < 0.05$
[2] $AUC_{0-\infty}$-for single dose and AUC_{12} for multiple dose data

[3] Harmonic Means

Pediatric Patients

Children with pharyngitis, otitis media or skin infections

Another study was conducted in pediatric patients and included again both a single dose phase (2 groups, non-fasting and fasting) and multiple dose phase (1 group, fasting) design. It was conducted in 28 infants and children ages 6 months to 10 years with pharyngitis, otitis media or skin infections. The single dose phase involved the administration of a single 7.5 mg/kg dose of clarithromycin granules for suspension (125 mg/5 mL) in either a non-fasting or fasting (2 hours before or 1.5 hours after eating) state.

In the multiple dose phase, patients were given multiple 7.5 mg/kg doses (every 12 hours for 4 or 5 days) of clarithromycin granules for suspension in a fasting state.

A summary of pharmacokinetic parameters is presented in Error! Reference source not found..

Table 6
Clarithromycin and 14-OH-Clarithromycin Pharmacokinetic Parameters in Pediatric Patients

Parameters	**Single Dose Fasting Mean ± SD**	**Single Dose Non-Fasting Mean ± SD**	**9th Dose b.i.d. Fasting Mean ± SD**
	(Group I)	(Group III)	(Group II)
Clarithromycin			
C_{max} (mcg/mL)	3.59 ± 1.47	4.58 ± 2.76	4.60 ± 2.08
T_{max} (hr)	3.1 ± 1.0	2.8 ± 0.7	2.8 ± 1.0
C_{min} (mcg/mL)	--	--	1.67 ± 1.44
Lag (hr)	0.6	0.4	--
AUC_6 (mcg•hr/mL)	10.0 ± 5.49	14.2 ± 9.39	15.7 ± 6.72
14-OH-Clarithromycin			
C_{max} (mcg/mL)	1.19 ± 0.37	1.26 ± 0.46	1.64 ± 0.75
T_{max} (hr)	3.2 ± 1.0	4.0 ± 1.0	2.7 ± 1.7
C_{min} (mcg/mL)	--	--	1.08 ± 0.84
Lag (hr)	0.6	0.7	--
AUC_6 (mcg•hr/mL)	3.66 ± 1.49	4.37 ± 1.79	6.69 ± 2.97

Mean peak plasma clarithromycin and 14-OH metabolite concentrations after single dose administration in a fasting state were 3.59 and 1.19 mg/L, respectively. The differences in C_{max} and AUC in the non-fasting and fasting group were not statistically significant. The study shows no deleterious effect of food co-administration on clarithromycin bioavailability in infants and children, similar to results previously noted in adults receiving the tablet formulation.

Mean peak plasma clarithromycin and 14-OH-clarithromycin concentrations after multiple dose (every 12 hours for 4 to 5 days) administration of 7.5 mg/kg of clarithromycin suspension in a

fasting state were 4.60 and 1.64 mg/L, respectively. These values compare favourably with those observed in adults after multiple oral dose administration of 250 and 500 mg of clarithromycin. C_{max} and AUC increase after multiple dosing as compared with values after single dose administration which is also comparable with data obtained in adults. This indicates that there is no unusual accumulation in infant and children.

Children with secretory otitis media

Multiple oral doses of clarithromycin (7.5 mg/kg every 12 hours for 7 days) were administered to 31 children ages 2 to 12 years with a diagnosis of secretory otitis media. Clarithromycin serum and middle ear effusion (MEE) concentrations were 1.73 ± 1.21 (range 0.16 to 4.96) mg/L and 2.53 ± 2.31 (range 0.39 to 10.62) mg/kg, respectively. In 16 of 24 patients MEE concentrations equaled or exceeded those in serum. The ratio of MEE to serum concentration was 2.48 ± 3.57 (range 0.19 to 15.31).

14-OH-clarithromycin serum and MEE concentrations were 0.82 ± 0.32 (range 0.26 to 1.53) mg/L and 1.27 ± 0.99 (range 0.24 to 4.20) mg/kg, respectively (**Error! Reference source not found.**). In 14 of 24 patients MEE concentrations equaled or exceeded those in serum. The ratio of MEE to serum concentration was 1.73 ± 1.4 (range 0.25 to 5.87).

Table 7
Clarithromycin Serum and Middle Ear Effusion Concentrations after clarithromycin 7.5 mg/kg q12 h for 5 doses

Analyte	Serum (mcg/mL)	Middle Ear Fluid (mcg/mL)
Clarithromycin	1.7	2.5
14-OH-Clarithromycin	0.8	1.3

When children (n = 10) were administered a single oral dose of 7.5 mg/kg suspension, food increased mean plasma clarithromycin concentration from 3.6 (± 1.5) mcg/mL to 4.6 (± 2.8) mcg/mL and the extent of absorption from 10.0 (± 5.5) mcg•hr/mL to 14.2 (± 9.4) mcg•hr/mL.

Although the onset and/or rate of absorption from the suspension formulation is significantly slower than that of the tablet formulation, this is of little clinical relevance.

11 STORAGE, STABILITY AND DISPOSAL

Taro-Clarithromycin (Clarithromycin for Oral suspension, USP)
Store dry powder at controlled room temperature 15° C to 30° C Protect from light. After reconstitution, store between (15ºC and 25ºC) and use within 14 days. Do not refrigerate.Discard after 14 days. The graduated syringe used for dosage administration should be rinsed between uses. Do not leave syringe in bottle. Do not store reconstituted suspension in syringe.

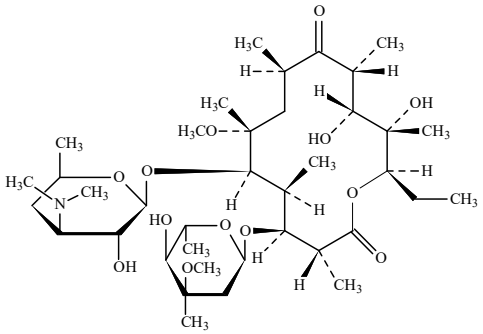
12 SPECIAL HANDLING INSTRUCTIONS

There are no further special handling instructions for this product (see 11 STORAGE, STABILITY AND DISPOSAL).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Clarithromycin
Chemical name:	(3R*, 4S*, 5S*, 6R*, 7R*, 9R*, 11R*, 12R*, 13S*, 14R*)-4-[(2,6-dideoxy-3-C-methyl-3-0-methyl-alpha-L-ribo-hexopyranosyl)oxy]-14-ethyl-12,13-dihydroxy-7-methoxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-beta-D-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2-10- dione.
Molecular formula and Molecular mass:	$C_{38}H_{69}NO_{13}$, 748 g/mol
Structural formula:	 **Clarithromycin**
Physicochemical properties:	Clarithromycin, USP is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in dehydrated alcohol, in methanol and in acetonitrile, practically insoluble in water. Slightly soluble in phosphate buffer at pH values 2 to 5. The partition coefficient of clarithromycin is influenced by the pH of the water phase and polarity of the organic phase. For octanol (dipole moment = 0.25): water, the partition co-efficient varies from 5.63 to 46.0 for pH water increases from 2 to 8. The melting point of clarithromycin is approximately 225°C.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

See 14 CLINICAL TRIALS, 14.2 Study Results - for trial design and study demographics by product and indication.

14.3 Comparative Bioavailability Studies

A randomized, two-way, single-dose, crossover comparative bioavailability study of TARO-CLARITHROMYCIN 125 mg/5 mL with BIAXIN® 125 mg/5 mL (Abbott Laboratories Ltd., Canada) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from the 23 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Clarithromycin 125 mg dose administered as 5 mL x 125 mg/5 mL oral suspension From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (ng-hr/mL)	4022.00 4304.74 (39.4)	4445.51 4637.90 (29.7)	90.83	84.61–97.50
$AUC_{0-\infty}$ (ng-hr/mL)	4187.36 4480.88 (39.2)	4597.58 4794.79 (29.6)	91.44	85.15–98.19
C_{max} (ng/mL)	672.93 705.63 (34.5)	782.21 808.30 (26.9)	86.14	79.02 – 93.90
T_{max}~ (h)	3.15 (25.5)	3.13 (22.9)	-	-
$T_{½}$~ (h)	4.32 (21.2)	4.21 (16.8)	-	-

* Taro-Clarithromycin 125 mg/5 ml oral suspension (Taro Pharmaceuticals Inc.)
†BIAXIN® (clarithromycin for oral suspension, USP) 125 mg/5 mL (Abbott Laboratories Limited, Canada) was purchased in Canada.
~Expressed as Arithmetic Mean (CV%) only

A randomized, two-way, single-dose, crossover comparative bioavailability study of TARO-CLARITHROMYCIN 250 mg/5 mL with BIAXIN® 250 mg/5 mL (Abbott Laboratories Ltd., Canada) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from the 20 subjects that were included in the statistical analysis are presented in the following table:

Summary Table of the Comparative Bioavailability Data
Clarithromycin (5 mL x 250 mg/5 ml oral suspension)
From measured data
Geometric Mean/Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-T} (µg-hr/mL)	12.52/13.46 (40.7)	13.19/14.17 (40.8)	94.92	87.78 – 102.63
AUC_{0-I} (µg-hr/mL)	12.97/13.90 (39.8)	13.72/14.72 (40.4)	94.56	87.73 – 101.91
C_{max} (ng/mL)	1.79/1.86 (29.4)	1.98/2.07 (31.6)	90.49	81.86 – 100.04
$T_{max}$$ (h)	3.33 (2.00 – 4.33)	3.17 (2.00 – 5.00)	-	-
$T_{½}$~ (h)	5.07 (15.5)	5.10 (19.2)	-	-

* Taro-Clarithromycin 250 mg/5 ml Oral Suspension (Taro Pharmaceuticals Inc.)
†BIAXIN® (clarithromycin for oral suspension, USP) 250 mg/5 mL (Abbott Laboratories Limited, Canada) was purchased in Canada.
$ Expressed as the Median (Range) only
~Expressed as Arithmetic Mean (CV%) only

A randomized, two-way, single-dose, crossover comparative bioavailability study of TARO-CLARITHROMYCIN 250 mg/5 mL with BIAXIN® 250 mg/5 mL (Abbott Laboratories Ltd., Canada) was conducted in healthy, adult, male subjects under high-fat, high-calorie fed conditions. Comparative bioavailability data from the 36 subjects that were included in the statistical analysis are presented in the following table:

Summary Table of the Comparative Bioavailability Data
Clarithromycin (5 mL x 250 mg/5 mL oral suspension)
From measured data
Geometric Mean/
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	90% Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_T (µg-hr/mL)	7.17/7.41 (25.68)	7.99/8.48 (34.61)	89.85	83.76 - 96.37
AUC_I (µg-hr/mL)	7.42/7.66 (25.19)	8.26/8.75 (34.23)	89.93	83.99 - 96.28
C_{max} (µg/mL)	0.83/0.86 (27.97)	0.94/1.00 (34.56)	88.34	81.54 - 95.71
T_{max}§ (h)	5.67 (2.67 – 9.00)	6.00 (2.67 – 10.00)	-	-
$T_{½}$€ (h)	5.35 (16.83)	5.27 (18.02)	-	-

* Taro-Clarithromycin 250 mg/5 ml oral suspension (Taro Pharmaceuticals Inc.)
† BIAXIN® (clarithromycin for oral suspension USP) 250 mg/5 mL (Abbott Laboratories Limited, Canada) was purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

Clarithromycin for Oral Suspension

Relative Bioavailability of Clarithromycin for Oral Suspension and Clarithromycin Tablet Formulations

Plasma concentrations of clarithromycin and 14-OH-clarithromycin were studied in 22 healthy male adult volunteers following administration of single 250 mg oral doses of clarithromycin as granules for suspension or as a 250 mg immediate-release tablet. Each participant received 3 clarithromycin regimens:

Regimen A: 250 mg (10 mL) clarithromycin oral suspension under non-fasting conditions (30 min after the start of breakfast)
Regimen B: 250 mg (10 mL) clarithromycin oral suspension under fasting conditions (2 hours before breakfast after a minimum 12 hour overnight fast)
Regimen C: one 250 mg immediate-release tablet under fasting conditions (2 hours before breakfast after a minimum 12-hour overnight fast)

Mean plasma concentrations of clarithromycin and 14-OH-clarithromycin are illustrated in **Figure 2**.

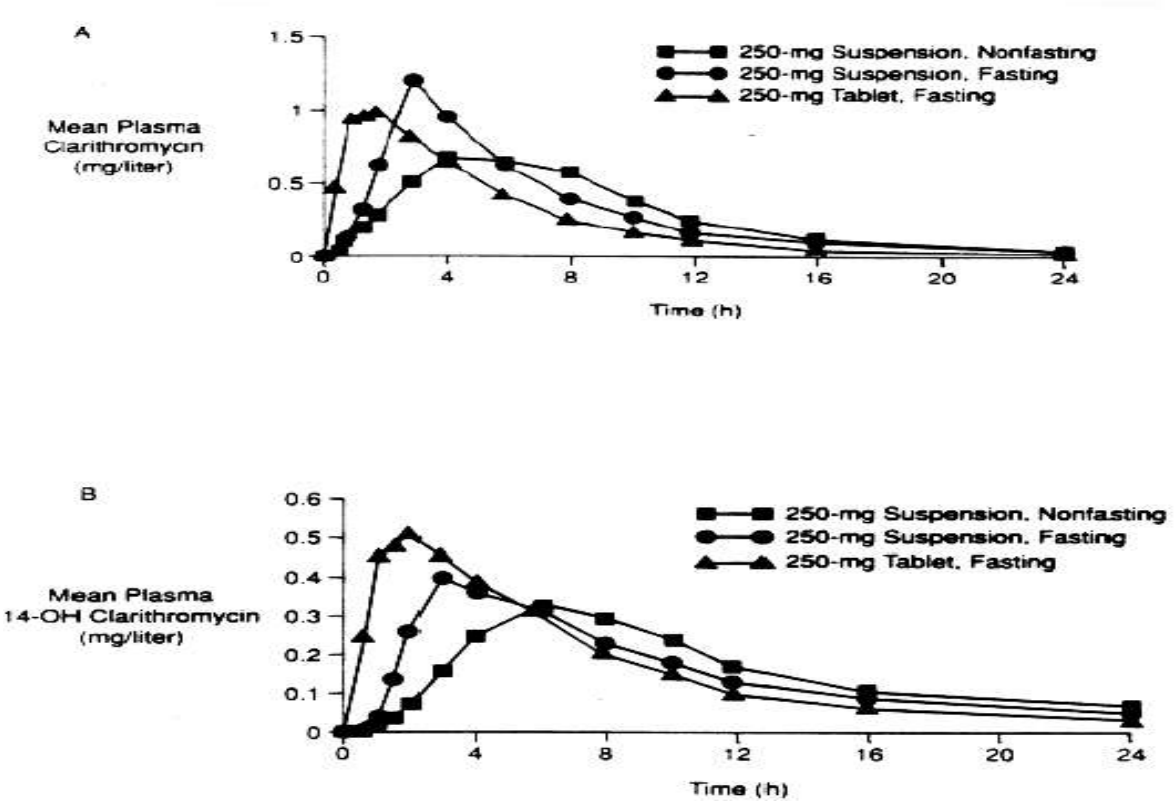


Figure 1: Mean Plasma Clarithromycin (A) and 14-OH-Clarithromycin (B) Concentration vs Time Data After Oral Administration of 250 mg of Clarithromycin

A summary of pharmacokinetic parameters is presented in **Table** .

Table 8
Comparative Single-Dose Bioavailability Data for Clarithromycin –(Clarithromycin for Oral Suspension) *versus* 250 mg (IR Tablet) under Fasting Conditions and the Effect of Food on the Bioavailability of Clarithromycin for Oral Suspension

Parameter	Arithmetic Mean (CV%)			Relative Bioavailability	
	Suspension Non-Fasting Regimen A	Suspension Fasting Regimen B	Tablet Fasting Regimen C	Point Estimate (%)+	90% Confidence Interval
Clarithromycin					
AUC_{τ} (mcg·h/mL)	6.52 (57)	7.23 (35)	6.33 (36)	A *vs.* B: 90.0 B *vs.* C: 114.0	77.5 – 102.4 99.8 – 128.2
C_{max} (mcg/mL)	0.95 (47)	1.24 (29)	1.10 (30)	A *vs.* B: 77.8 B *vs.* C: 112.1	63.8 – 91.8 96.4 – 127.8
C_{min} (mcg/mL)	5.3 (36)	3.3 (35)	1.7 (36)	--	--
T_{max} (hr)	3.7	3.7	3.3	--	--
14(R)-Hydroxy-Clarithromycin					
AUCτ (mcg·h/mL)	4.26 (35)	4.65 (25)	4.92 (29)	A *vs.* B: 91.1 B *vs.* C: 93.9	78.5 – 103.7 82.1 – 105.7
C_{max} (mcg/mL)	0.38 (30)	0.42 (34)	0.55 (32)	A *vs.* B: 90.4 B *vs.* C: 76.1	77.3 – 103.5 66.1 – 86.0
T_{max} (hr)	5.8 (27)	3.4 (36)	1.9 (30)	--	--
$t_{1/2}$ (hr)	6.7	7.9	6.9	--	--

Regimen A = 250 mg (10 mL) clarithromycin oral suspension under non-fasting conditions (30 min after the start of breakfast).
Regimen B = 250 mg (10 mL) clarithromycin oral suspension under fasting conditions (2 hours before breakfast after a minimum 12-hour overnight fast).
Regimen C= 250 mg clarithromycin IR tablet under non-fasting conditions (30 min after the start of breakfast).
* Harmonic mean half-life.
+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.
Legend: IR = immediate-release

The relative bioavailability of the oral suspension formulation compared with the tablet can be seen by comparing Regimen B *versus* Regimen C. The difference in clarithromycin T_{max} (3.30 ± 1.20 vs.1.70 ± 0.60 hr) with the oral suspension and tablet formulations, respectively, shows that the onset and/or rate of absorption from the suspension is slower. A similar trend is seen with the 14-OH metabolite. For clarithromycin, C_{max} was not significantly different between the formulations but for the 14-OH metabolite, C_{max} after suspension administration was significantly lower than after tablet administration. The extent of absorption of clarithromycin was not significantly different from that of the tablet as assessed by AUC, whereas for the 14-OH metabolite, the tablet formulation was associated with a significantly higher extent of metabolite formation than the suspension formulation.

The difference between clarithromycin T_{max} values under non-fasting and fasting conditions (Regimens A and B) was 5.30 ± 1.90 *versus* 3.30 ± 1.20 hr, respectively, and was similar for 14-OH-clarithromycin (5.80 ± 1.60 *vs.* 3.40 ± 1.20 hr). Therefore, the onset and/or rate of absorption from the suspension formulation is slowed by the presence of food.

For clarithromycin, C_{max} was significantly higher under fasting than under non-fasting conditions. The extent of absorption of clarithromycin and formation of 14-OH-clarithromycin

were not significantly different between fasting and the non-fasting conditions as assessed using AUC.

Single- and multiple-dose adult volunteer studies have established that the suspension and tablet formulations have similar pharmacokinetics.

15 MICROBIOLOGY

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

Clarithromycin is active *in vitro* against various aerobic and anaerobic gram-positive and gram-negative organisms as well as most MAC microorganisms. The *in vitro* activity of clarithromycin is presented in **Table** .

Additionally, the 14-OH-clarithromycin metabolite also has significant antimicrobial activity which may be additive to the activity of the parent compound. Against *Haemophilus influenzae*, 14-OH clarithromycin is twice as active as the parent compound *in vitro*. However, for MAC isolates, the 14-OH metabolite was 4 to 7 times less active than clarithromycin. The clinical significance of this activity against MAC is unknown.

Clarithromycin is bactericidal to *H. pylori*; this activity is greater at neutral pH than at acid pH.

The ranges of MICs of clarithromycin, 14-OH-clarithromycin metabolite and the MICs required to inhibit 50% (MIC_{50}) and 90% (MIC_{90}) of bacteria are presented in **Table** and **Table** . Beta-lactamase production should not have any effect on clarithromycin activity.

Cross-resistance to azithromycin has been documented. Attention should be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

The *in vitro* data indicate enterobacteriaceae, pseudomonas species and other non-lactose fermenting gram negative bacilli are not sensitive to clarithromycin.

Clarithromycin has been shown to be active against most strains of the following micro-organisms both *in vitro* and in clinical infections as described in the **1 INDICATIONS** section:

Aerobic Gram-Positive microorganisms	**Aerobic Gram-negative microorganisms**	**Other microorganisms**	**Mycobacteria**
Staphylococcus aureus *Streptococcus pneumoniae* *Streptococcus pyogenes*	*Haemophilus influenzae* *Haemophilus parainfluenzae* *Moraxella catarrhalis*	*Mycoplasma pneumoniae* *Chlamydia pneumoniae* (TWAR)	*Mycobacterium avium complex* (MAC) consisting of: *Mycobacterium avium* *Mycobacterium Intracellulare*

The following *in vitro* data are available, **but their clinical significance is unknown**. Clarithromycin exhibits *in vitro* activity against most strains of the following microorganisms; however, the safety and effectiveness of clarithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials (See **15** MICROBIOLOGY, Tables 13-15 below):

Aerobic Gram-positive microorganisms	Aerobic Gram-negative microorganisms	Anaerobic Gram-positive microorganisms	Anaerobic Gram-negative microorganisms	Campylobacter
Streptococcus agalactiae *Viridans group streptococci*	*Bordetella pertussis* *Pasteurella multocida*	*Clostridium perfringens* *Propionibacterium acnes*	*Bacteroides melaninogenicus*	*Campylobacter jejuni*

Table 13
***In Vitro* Susceptibility® of Strains of Gram-Positive and Gram-Negative Bacteria to Clarithromycin**

Microorganisms	Number of Strains	Cumulative % of Strains Inhibited at MIC (mg/L)											
		.031	.062	.125	.250	.500	1.00	2.00	4.00	8.00	16.0	32.0	64.0
Gram Positive													
Staphylococcus aureus methicillin resistant	25	-	4	4	8	8	12	12	12	12	12	12	100
Staphylococcus aureus methicillin susceptible	126	-	20	75	84	86	87	87	87	88	88	88	100
All *Staphylococcus aureus*	151	-	17	63	72	73	74	74	74	75	75	75	100
Staphylococcus epidermidis	59	-	18	37	42	44	45	47	50	50	54	54	100
Other coagulase negative *staphylococcus*	27	-	14	44	44	48	48	48	55	55	59	59	100
Streptococcus pyogenes (GrA)	48	89	91	93	97	97	97	100	-	-	-	-	-
Enterococcus	97	1	4	8	25	59	61	63	63	64	64	68	100
Streptococcus pneumoniae	26	38	84	84	84	100	-	-	-	-	-	-	-
Streptococcus agalactiae (GrB)	41	95	95	95	95	95	97	100	-	-	-	-	-
Streptococcus viridans	15	86	86	86	93	93	93	93	93	93	93	93	100
Other β-hemolytic Streptococcus	19	78	78	78	84	84	84	89	89	94	94	94	100
Corynebacterium species	11	27	45	54	63	63	63	81	81	90	100	-	-
Listeria monocytogenes	7	28	100	-	-	-	-	-		-	-	-	-
Gram Negative													
Neisseria gonorrhoeae	39	23	35	64	100	-	-	-	-	-	-	-	-
Haemophilus influenzae	56	3	3	3	7	16	37	80	100	-	-	-	-
Neisseria meningitides	6	-	33	50	83	100	-	-	-	-	-	-	-
Campylobacter species	30	-	10	10	43	80	93	100	-	-	-	-	-

* MICs do not take into account the antimicrobial activity of the 14-OH-clarithromycin metabolite.

Table 9 *In vitro* Susceptibility of Different Bacteria to Clarithromycin				
Microorganisms	**Number of strains**		**MIC (mg/L)**	
		Range	**50%**	**90%**
Mycoplasma pneumoniae	30	≤ 0.004-0.125	≤ 0.004	≤ 0.031
Bordetella pertussis	18	≤0.008-0.06	≤0.008	0.03
Legionella pneumophila	14	0.12-0.25	0.12	0.25
Haemophilus influenzae	22	2-8	4	8
Moraxella catarrhalis	17	0.03-0.25	0.06	0.25
Chlamydia trachomatis	11	0.002-0.008	0.004	0.008
Neisseria gonorrhoea	26	0.0625-4	0.125	0.5
Mycobacterium avium	30	4-32	8	16
Mycobacterium avium-intracellulare	124	< 0.25-4	1	2
Mycobacterium chelonae	137	-- --		0.25
Mycobacterium fortuitum	86	--	2.0	>8.0
Mycobacterium kansassi	24	≤0.125-0.25	≤0.125	0.25
Pasteurella multocida	10	1.0-4	1.0	2.0
Bacteriodes melaninogenicus	12	≤0.125-0.2	≤0.125	≤0.125
Clostridium perfringens	10	0.25-0.5	0.5	0.5
Staphylococcus aureus (methicillin sensitive)	20	0.06-0.25	0.17	0.24
Streptococcus pyogenes	10	≤ 0.06	≤ 0.06	≤ 0.06
Chlamydia pneumoniae	49	0.004-0.025	0.016	0.031
Helicobacter pylori †	13	0.03-0.06	0.03	0.03

† **Hardy DJ, Hanson CW, Hensey DM, Beyer JM, Fernandes PB. Susceptibility of Campylobacter pylori to macrolides and fluoroquinolones. J Antimicrob Chemother 1988;22:631-636.**

Table 10 *In vitro* Susceptibility of Different Bacteria to 14-OH-Clarithromycin				
Microorganisms	**Number of strains**		**MIC (mg/L)**	
		Range	**50%**	**90%**
Streptococcus pyogenes	15	0.015-0.03	0.015	0.03
Streptococcus pneumoniae	13	≤ 0.004-0.015	0.008	0.015
Streptococcus agalactiae	15	0.03-0.06	0.06	0.06
Listeria monocytogenes	14	0.25-0.5	0.5	0.5
Moraxella catarrhalis	17	0.03-0.12	0.06	0.12
Neisseria gonorrhoeae	15	0.06-1	0.25	0.5
Campylobacter jejuni	12	0.25-2	0.5	2
Legionella pneumophila	14	0.12-0.5	0.25	0.5
Haemophilus influenzae	22	1-4	2	4
Bordetella pertussis	18	≤0.008-0.06	0.015	0.06
Bacteroides fragilis	10	0.5->128	1	1
Clostridium perfringens	10	0.5-0.5	0.5	0.5
Propionibacterium acnes	12	0.03->128	0.03	0.06

Clarithromycin Kill Kinetics Against *Helicobacter pylori*

Figure illustrates the kill kinetics of clarithromycin and 14-OH-clarithromycin against *H. pylori* at 8 × MIC and at pH 8.0; and **Figure** illustrates the kill kinetics of clarithromycin and amoxicillin against *H. pylori* at pH 6.5.

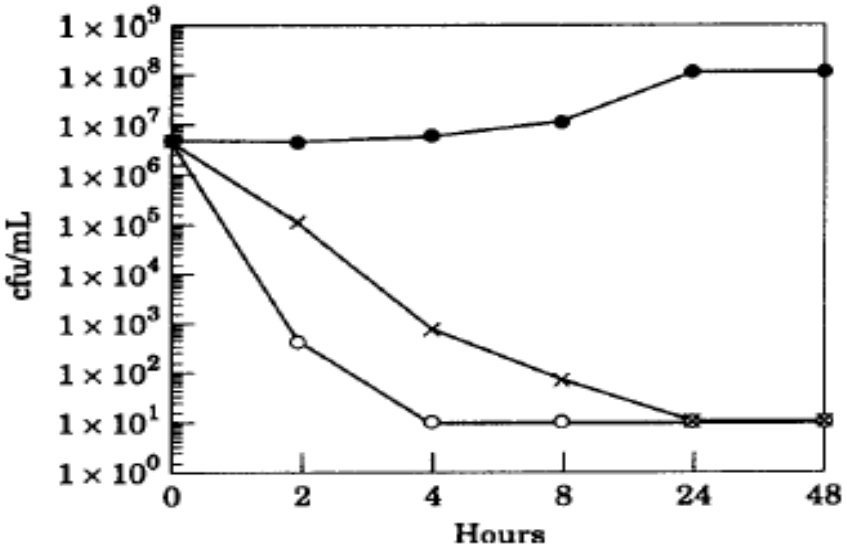


Figure 3: Kill kinetics of clarithromycin and 14-OH-clarithromycin against H. pylori strain 2597 at 8 × MIC and at pH 8.0. A flask was inoculated to produce a starting inoculum of approximately 106 cfu/mL. The flask was then incubated in an anaerobe jar with CampyPak® and shaken gently at 37°C. Counts were done at 0, 2, 4, 8, 24, and 48 h in physiological saline after 72 h incubation. ●, No antimicrobial; o, clarithromycin (0.12 mg/L); x, 14-OH-clarithromycin (0.24 mg/L).

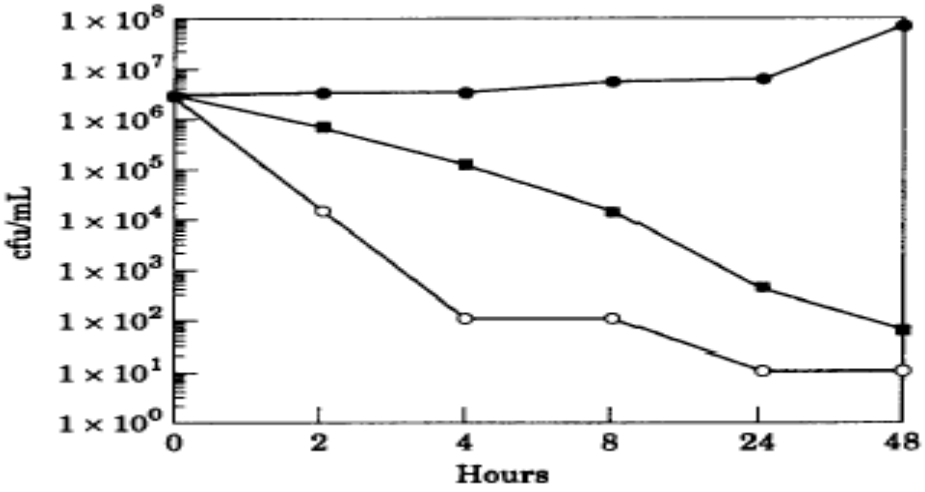


Figure 4: Kill kinetics of clarithromycin and amoxicillin against *H. pylori* strain 2597 at pH 6.5. Counts were done at 0, 2, 4, 8, 24, and 48 h in physiological saline after 72 h incubation. No antimicrobial; o, clarithromycin (3 mg/L); ■, amoxicillin (3 mg/L)

Susceptibility Testing excluding *Mycobacteria* and *Helicobacter*

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[43] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of clarithromycin powder.

The standard single disc susceptibility test (using the 15 mcg clarithromycin disc) and the dilution susceptibility test should be interpreted according to the criteria in **Table** .

Table 16
Criteria for the Interpretation of Standard Single Disc and Dilution Susceptibility Tests except for *H. influenzae* and *H. pylori*

	Zone Diameter (mm)	Appropriate MIC Correlate (mg/L)
Susceptible	≥ 18	≤ 2
Intermediate*	14 to 17	4
Resistant	≤ 13	≥ 8

*Indicates that the test results are equivocal; therefore, dilution tests may be indicated.
N.B. These criteria and the definition are in agreement with NCCLS. Documents M2-A6[44] and M100-S8[45].

The standard single disc susceptibility test (using the 15 mcg clarithromycin disc) for *H. Influenzae* should be interpreted according to the criteria in **Table** .

Table 11 Criteria for the Interpretation of Standard Single Disc and Dilution Susceptibility Tests for *H. influenzae*

	Zone Diameter (mm)	Appropriate MIC Correlate (mg/L)
Susceptible	≥ 13	≤ 8
Intermediate*	11 to 12	16
Resistant	≤ 10	≥ 32

*Indicates that the test results are equivocal; therefore, dilution tests may be indicated.
N.B. According to the revised NCCLS 1997 and 1998 Guidelines, the zone diameter and MIC values reflect both the activities of the parent compound and 14-OH metabolite.

A report of "Susceptible" indicates that the pathogen is likely to respond to monotherapy with clarithromycin.

A report of "Intermediate" indicates that the result be considered equivocal, and if the microorganism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where clarithromycin is physiologically concentrated or in situations where high clarithromycin dosages can be used. This category provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretations.

A report of "Resistant" indicates that achievable drug concentrations are unlikely to be inhibitory, and other therapy should be selected.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[44] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15-mcg clarithromycin to test the susceptibility of microorganisms to clarithromycin.

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

Standardized Dilution Techniques

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin powder should provide the following MIC values for *S. aureus* and *H. influenzae* (**Table 18**).

Table 18
Standard Clarithromycin Powder MIC Values

Microorganisms		MIC (mcg/mL)
S. aureus	ATCC 29213	0.12 to 0.5
H. influenzae	ATCC 49247	4 to 16

Standardized Diffusion Techniques

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15-mcg clarithromycin disk should provide the following zone diameters for *S. aureus* and *H. influenzae* (**Table**).

Table 19
Zone Diameter for the 15 mcg Clarithromycin Disc

Microorganisms		Zone Diameter (mm)
S. aureus	ATCC 25923	26 to 32
H. influenzae	ATCC 49247	11 to 17

In vitro Activity of Clarithromycin against Mycobacteria

Clarithromycin has demonstrated *in vitro* activity against MAC microorganisms isolated from both AIDS and non-AIDS patients. While gene probe techniques may be used to distinguish *M. avium* species from *M. intracellulare*, many studies only reported results on MAC isolates.

Various *in vitro* methodologies employing broth or solid media at different pH's, with and without oleic acid-albumin-dextrose-catalase (OADC), have been used to determine clarithromycin MIC values for mycobacterial species. In general, MIC values decrease more than 16-fold as the pH of Middlebrook 7H12 broth increases from 5.0 to 7.4. At pH 7.4, MIC values determined with Mueller-Hinton agar were 4- to 8-fold higher than those observed with Middlebrook 7H12 media. Utilization of OADC in these assays has been shown to further alter MIC values.

Clarithromycin activity against 80 MAC isolates from AIDS patients and 211 MAC isolates from non-AIDS patients was evaluated using a microdilution method with Middlebrook 7H9 broth. Results showed MIC values of ≤ 4.0 mcg/mL in 81% and 89% of the AIDS and non-AIDS MAC isolates, respectively. Twelve percent of the non-AIDS isolates had an MIC value ≤ 0.5 mcg/mL. Clarithromycin activity was evaluated against phagocytized MAC in mouse and human macrophage cell cultures as well as in the beige mouse infection model.

Clarithromycin activity was evaluated against *Mycobacterium tuberculosis* microorganisms. In 1 study utilizing the agar dilution method with Middlebrook 7H10 media, 3 of 30 clinical isolates had an MIC of 2.5 mcg/mL. Clarithromycin inhibited all isolates at > 10.0 mcg/mL.

Susceptibility Testing for *Mycobacterium avium* Complex

The disk diffusion and dilution techniques for susceptibility testing against gram-positive and gram-negative bacteria should not be used for determining clarithromycin MIC values against mycobacteria. *In vitro* susceptibility testing methods and diagnostic products currently available for determining MIC values against MAC organisms have not been standardized nor validated. Clarithromycin MIC values will vary depending on the susceptibility testing method employed, composition and pH of the media, and the utilization of nutritional supplements. Breakpoints to determine whether clinical isolates of *M. avium* or *M. intracellulare* are susceptible or resistant to clarithromycin have not been established.

In vitro Activity of Clarithromycin against *Helicobacter pylori*

Clarithromycin has demonstrated *in vitro* activity against *H. pylori* isolated from patients with duodenal ulcers. *In vitro* susceptibility testing methods (broth microdilution, agar dilution, E-test, and disk diffusion) and diagnostic products currently available for determining MICs and zone sizes have not been standardized, validated, or approved for testing *H. pylori*. The clarithromycin MIC values and zone sizes will vary depending on the susceptibility testing methodology employed, media, growth additives, pH, inoculum concentration tested, growth phase, incubation atmosphere, and time.

Susceptibility Test for *Helicobacter pylori*

In vitro susceptibility testing methods and diagnostic products currently available for determining MICs and zone sizes have not been standardized, validated, or approved for testing *H. pylori* microorganisms. MIC values for *H. pylori* isolates collected during 2 U.S. clinical trials evaluating clarithromycin plus omeprazole were determined by broth microdilution MIC methodology (Hachem CY *et al*., 1996). Results obtained during the clarithromycin plus omeprazole clinical trials fell into a distinct bimodal distribution of susceptible and resistant clarithromycin MICs.

If the broth microdilution MIC methodology published in Hachem CY *et al*., 1996 is used and the following tentative breakpoints are employed, there should be reasonable correlation between MIC results and clinical and microbiological outcomes for patients treated with clarithromycin plus omeprazole (**Table 20**).

Table 20
Susceptibility Testing for *Helicobacter pylori* in Patients Treated with Clarithromycin and Omeprazole

MIC (mcg/mL)	Interpretatio
≤ 0.06	Susceptible
0.12 to 2.0	Intermediate
≥ 4	Resistant (R)

These breakpoints should not be used to interpret results obtained using alternative methods.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Chronic Toxicity

Carcinogenicity

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

Mutagenicity

The following *in vitro* mutagenicity tests have been conducted with clarithromycin: *Salmonella*/mammalian microsome test, bacterial induced mutation frequency test, *in vitro* chromosome aberration test, rat hepatocyte DNA synthesis assay, mouse lymphoma assay, mouse dominant lethal study, mouse micronucleus test.

All tests had negative results except the *in vitro* chromosome aberration test which was weakly positive in one test and negative in another. In addition, a Bacterial Reverse-Mutation Test (Ames Test) has been performed on clarithromycin metabolites with negative results.

Reproduction and Developmental Toxicology:

Fertility and reproduction studies have shown that daily doses of 150 to160 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 2 times the human serum levels.

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

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

Special Toxicology:

Acute Renal Toxicity

There was no evidence of nephrotoxicity of clarithromycin in the rat at doses up to 500 mg/kg/day.

Hepatotoxicity

In the *in vitro* and *in vivo* hepatotoxicity studies comparing clarithromycin with erythromycin, it was found that clarithromycin caused no greater cytotoxicity than erythromycin stearate and much less toxicity than erythromycin estolate. Hepatic enzyme induction was not found in doses below 500 mg/kg/day. In cynomolgus monkeys, the closest metabolic model for humans, elevations of ALT and LDH were identified at 200 mg/kg/day.

In dogs, a rise of ALT has been seen at 100 mg/kg/day, and in Wistar rats, a similar elevation of enzymes was seen at 200 mg/kg/day. Morphologic lesions related to prolonged exposure to clarithromycin (up to 6 months) have been consistent with reportedly reversible changes in rat, dog and monkey studies. Such doses are many times beyond the therapeutic range in humans, which is within 8 to 10 mg/kg/day.

Ocular Toxicity

Ocular lesions appear confined to dogs and monkeys receiving lethal doses, which were large multiples of the human therapeutic dose. Radiolabelled clarithromycin studies indicate the eye is not selectively burdened by drug deposits and that clearance from this tissue follows that seen in other tissues. Opacities occur in the cornea following widespread extraocular tissue changes which are detectable via numerous diagnostic methods. Reduced intraocular pressure precedes

corneal opacity in a relatively predictive manner. Some evidence for transient opacity and at least partial resolution was noted in animal studies, but most animals succumbed to other organ dysfunctions shortly after opacities were observed.

Animals given doses close to the therapeutic dose had no ocular changes. No ophthalmologic effects were noted in rabbits treated at doses of 40 and 160 mg/kg/day for 28 days.

Ototoxicity

No effects on pinna reflex were seen in guinea pigs at a dose of 400 mg/kg/day but inner and outer hair cells disappeared suggesting toxic damage. No evidence of damage was reported at 200 mg/kg/day.

Juvenile Toxicity

Clarithromycin was administered orally to rats and mice 3 days after birth. The study design was 10M/10F animals in the dose groups, 20M/20F in the control group. The animals were dosed by gavage with a single dose of a suspension of clarithromycin in 5% gum arabic; control animals received a solution of 5% gum arabic. The recovery period was 14 days.

Mice

The mice were dosed at 714, 857, 1028, 1233, 1480 and 1776 mg/kg; the rats at 769, 1000, 1300, 1690, 2197 and 3713 mg/kg.

LD_{50} (95% confidence limits) in mice was 1290 mg/kg (1170 to 1420 mg/kg) in males and 1230 mg/kg (1130 to 1340 mg/kg) in females; the sex difference was considered to be negligible.

LD_{50} of clarithromycin orally administered to adult mice is about 2700 mg/kg; acute toxicity was more notable in juvenile animals than in adults. The LD_{50} of antibiotics of the penicillin group, cephalosporin group and macrolide group is generally lower in juvenile animals than in adults; clarithromycin showed similar results.

Body weight was reduced or its increase was suppressed in both males and females of each dosing group from 1 to 4, 7 or 9 days after the administration, but its changes thereafter were comparable to those in the control group.

Some animals died from 1 to 7 days after the administration. The general condition, suckling behaviour and spontaneous movements were depressed in some of the mice administered 1028 mg/kg or more clarithromycin from 1 day after the administration, but these changes disappeared by 7 days after the administration in those that survived the observation period.

Necropsy of those that died spontaneously disclosed dark reddish lungs in more than half the animals. This finding suggests that the death in these animals was due to debilitation resulting from reduced suckling behaviour.

In the survivors, necropsy showed dilation of renal pelvis in 1 male of the 1028 mg/kg group and hypoplasia of the kidney in 1 female of the 1233 mg/kg group, but these uncommon conditions are considered to be incidental.

Rats

LD_{50} (95% confidence limits) in rats was 1330 mg/kg (1210 to 1470 mg/kg) in males and 1270 mg/kg (1150 to 1400 mg/kg) in females, the sex difference was considered to be negligible.

LD_{50} of the agent administered orally to adult rats is about 3000 mg/kg; the acute toxicity was more notable in juvenile animals than in adult animals. LD_{50} of antibiotics of the penicillin group, cephalosporin group, and macrolide group is generally lower in juvenile animals than in adult animals; clarithromycin showed similar results.

The body weight was reduced or its increase was suppressed in both males and females of each dosing group from 1 to 4 or 7 days after the administration, but body weight changes thereafter were comparable to those of the control group.

Some of the animals of both sexes died from 2 to 5 days after the administration. The general condition, suckling behaviour and spontaneous movements were depressed in some animals from 1 or 2 days after the administration, but in survivors these changes disappeared by 13 days after the administration. In the control group, 1 male and female of the same litter showed depressed suckling behaviour and spontaneous movements from 13 days after the administration, and the female was cannibalised by its mother 14 days after the administration. This is considered to be due to the death of all the other animals of the litter and a resultant reduction in the nursing activity of the mother.

Necropsy of those that died spontaneously showed dark-reddish lungs in about 25%. A reddish-black substance was noted in the intestines of a few males and females of each group administered 2197 mg/kg or more clarithromycin, probably because of bleeding from the intestines. From these findings, the deaths were considered to be due to debilitation resulting from depressed suckling behaviour or bleeding from the intestines.

Necropsy of the survivors revealed nodulated ribs in 1 male of the control group. Since this animal showed a reduction in body weight from 11 days after the administration, these nodules are considered to have been caused by suppressed development of the ribs associated with a delay in the growth. White spots in the liver surface of the 769 mg/kg and 1300 mg/kg groups, and a bulging mass on the surface of the liver and adhesion of the liver to the diaphragm were observed in 1 female of the 769 mg/kg group. Since these changes were infrequent and were not observed in the animals that died during the observation period, they are considered to be incidental.

Three clarithromycin pediatric formulations under consideration for development, a carbopol complex, a hot melt sprayed coating form and a spray-congealed dosage form, were evaluated for acute oral toxicity in rats. Five male and 5 females were administered a single oral dose of 1 of 3 clarithromycin pediatric formulations at a concentration of 250 mg/mL. The dose for all rats

was 20 mL/kg (i.e., 5 g/kg). Except for one rat considered to have been misdosed with the spray congealed dosage form, none of the rats died and no signs of toxicity were observed.

No gross morphologic changes were found when the rats were killed and necropsied 2 weeks after treatment.

Doses greater than 5 g/kg were considered to be excessive (5 g/kg is generally employed as the highest test dose for test materials with toxicity too low to determine the minimum lethal dose). Thus, clarithromycin pediatric formulations were found to be non-toxic to rats at the applicable maximum dose of 5 g/kg.

Rats

Two-week toxicity study was done with clarithromycin granules administered orally to preweaning rats. Crl:CD*(SD)BR pups, 5 days old at the start of treatment, were dosed by oral gavage with suspension for 17 to 20 days (**Table 21**).

Table 21
Subchronic Toxicity Study with Clarithromycin Granules Administered Orally to Crl:CD*(SD)BR Preweaning Rats (17 to 20 Treatment Days)

Treatment Group	Test Material	Dosages[a] (mg/kg/day)	Concentration[b] (mg/mL)	No/Group	
				M	F
T_o	Vehicle[c]	0	0	10	10
T_1	Clarithromycin Granule for Suspension	15	2.46	10	10
T_2	Clarithromycin Granule for Suspension	55	9.02	10	10
T_3	Clarithromycin Granule for Suspension	200	32.79	10	10

[a] Dosages are expressed in terms of the free base.
[b] In terms of bulk granule (a potency of 610 mcg/mg).
[c] 0.2% hydroxypropylmethylcellulose (HPMC).

One female pup in the vehicle Control group was found dead on day 18. Sporadic incidence of reddish spots on the skin or skin erythema occurred in some T_3 pups. The mean weight gains from days 0 to 17 for T_3 males and females were approximately 20 and 10% less than those of T_o males and females, respectively. There were no ophthalmic effects. Statistically significant decreases occurred in the values of mean hemoglobin, mean cell hemoglobin and mean cell volume of T_3 male pups (200 mg/kg/day); T_3 female pups (200 mg/kg/day) had lower hemoglobin and hematocrit values when compared to controls, but the differences were not significant; similarly the mean hematocrit value of the T_3 male pups was also lower than that of the controls. A statistically significant increase was observed in the mean relative kidney weights of T_3 pups when compared to controls. Treatment-related minimal to mild multifocal vacuolar degeneration of the intrahepatic bile duct epithelium and an increased incidence of nephritic lesions were observed in the T_3 pups (200 mg/kg/day).

A dosage of 200 mg/kg/day for 2 weeks produced decreased body weight gain, decreased mean hemoglobin and hematocrit values as well as histopathologic changes in the livers and kidneys of

preweaning rats. The "no-toxic-effect" dosage in this 2-week preweaning rat study was judged to be 55 mg/kg/day. This finding is similar to that reported following administration to adult rats for 1 month. Preweaning rats did not therefore appear to be more susceptible than mature rats.

Crl:CD*(SD)BR immature rats, aged 15 days at the start of treatment, were dosed daily orally by gavage for 6 weeks. The rats were dosed at 0, 15, 50 and 150 mg/kg clarithromycin, with 10 male and 10 female animals allocated to each treatment group. The control group was treated with 0.2% hydroxypropylmethylcellulose (HPMC) vehicle only.

No deaths occurred during the study. No drug-induced signs were observed. Male T_3 pups had a consistently lower mean body weight than male T_o pups on the growth curves. This is considered to be a drug-related effect. Male T_3 rats had lower mean food consumption than male T_o rats; male and female T_2 rats appear to have consistently higher mean food consumption than male and female T_o rats (not statistically significant). The following increases in relative mean organ weights were observed: liver and kidney of male and female T_3 rats, kidney of male T_1 rats and spleen of female T_3 rats. The increases in liver and kidney relative weights of male and female T_3 rats were considered to be drug induced, but no concurrent drug-related micropathology was observed.

Renal hydronephrosis occurred in 1 female T_2 rat, which was not considered to be drug-related. A small number of microscopic alterations was distributed randomly through control and treatment groups. None were drug-related.

The "no-toxic effect" level was considered to be 50 mg/kg/day. This finding is similar to administration of clarithromycin to adult rats for 1 month. Immature rats did not, therefore, appear to be more susceptible to clarithromycin than mature rats.
Crl:CD*(SD)BR juvenile rats, 16 days old at the start of treatment, were dosed by oral gavage for 42 to 44 treatment days (**Table 22**).

Table 22
Subchronic Toxicity Study with Clarithromycin Granules Administered Orally to Crl:CD*(SD)BR Juvenile Rats (42 to 44 treatment days)

Treatment Group	Test Material	Dosages[a] (mg/kg/day)	Concentration[b] (mg/mL)	No/Group	
				M	F
T_o	Vehicle[c]	0	0	10	10
T_1	Clarithromycin Granule for Suspension	15	2.44	10	10
T_2	Clarithromycin Granule for Suspension	50	8.13	10	10
T_3	Clarithromycin Granule for Suspension	150	24.4	10	10

[a] Dosages are expressed in terms of the free base.
[b] In terms of bulk granule, Clarithromycin Granule for Suspension with a potency of 615 mcg/mg.
[c] 0.2% hydroxypropylmethylcellulose (HPMC).

There were no deaths in the study. Excessive salivation occurred in some T_3 rats (1 to 2 hours after dosing) during the last 3 weeks of treatment. Male and female pups given 150 mg/kg/day (T_3) consistently had lower mean body weights than controls throughout the treatment period. The differences were statistically significant during the first 3 weeks of treatment. The mean weight gains from days 0 to 40 for T_3 males and females were 9.4 and 6.9% less than those of T_o males and females, respectively. There were no significant differences between control and drug-treatment groups in food consumption. There were no treatment-related ophthalmic effects.

No meaningful differences were found in urinalyses and hematology parameters for the drug-treated and control rats.

There was a statistically significant decrease in the mean albumin values of T_3 male and female rats when compared to controls and a statistically significant increase in the mean relative liver weights for T_3 rats when compared to controls. No treatment-related gross or microscopic observations were found. A dosage of 150 mg/kg/day produced slight toxicity in the treated rats. Therefore the no-effect dosage was judged to be 50 mg/kg/day.

Wistar rats, 4 days old at the start of treatment, were dosed by oral gavage for 28 treatment days followed by a 28-day recovery period (**Table 212**).

Table 212
Subchronic Toxicity Study with Clarithromycin Granules Administered Orally to Wistar Rats (28 treatment days)

Treatment Group	Test Material	Dosages[a] (mg/kg/day)	No/Group	
			M	F
T_o	Vehicle[b]	0	20	20
T_1	Clarithromycin	12.5	12	12
T_2	Clarithromycin	50	20	20
T_3	Clarithromycin	200	20	20

[a] Dosages are expressed in terms of the free base.
[b] 5% Gum Arabic.

No deaths or abnormalities in the general condition of the animals occurred during the administration or recovery periods in all treated groups.

Body weight gain was suppressed in males and females of the 200 mg/kg group from the 4th day of administration, but normal body weight gain was restored by the discontinuation of the administration. Urinalysis showed slight elevation in pH of the groups administered 50 mg/kg or more clarithromycin, but it was normalized after discontinuation of the administration.

Hematological examinations showed a reduction in haematocrit and a reduction in hemoglobin in both sexes, a reduction in MCHC in males, and a reduction in MCH in females of the 200 mg/kg group. Platelets were reduced in males of the 200 mg/kg group and females of all dosing groups, and white blood cells were reduced in both sexes of the 200 mg/kg group. These changes, however, were reversed or reduced by discontinuation of the administration.

Serum biochemical analyses revealed reduction in AST, ALP, total protein, and albumin in both sexes, a reduction in the calcium level in males, and an elevation in the blood glucose level and reduction in the creatinine level in females of the 200 mg/kg group. These changes, however, could be reversed by discontinuation of the administration.

Necropsy revealed no abnormalities in any of the groups. Concerning organ weights, the absolute and relative weights of the thymus were reduced in males and females of the 200 mg/kg group, but normal weights were restored by discontinuation of the administration.

Changes considered to be related to suppression of body weight gains were observed in the brain, lungs, heart (males only), liver, spleen, kidneys, caecum, and testes (males only) in both sexes of the 200 mg/kg/group. The weight of these organs recovered after discontinuation of the administration. Histopathological studies showed no changes considered to be related to the administration of clarithromycin.

Dogs

Clarithromycin was administered to juvenile beagles by oral catheter daily for 4 weeks at doses of 0 (Control), 30, 100 and 300 mg/kg, followed by a 4-week withdrawal period to evaluate recovery. At the start of the study the beagles were 3 weeks old; each group consisted of 3 males and 3 females; and 1 female and male were added to the control and high-dose groups for the recovery study.

None of the animals died during the administration or recovery period, and no changes in the general condition of the animals were observed.

No changes considered to be due to the administration of clarithromycin were observed in the food consumption, body weight, or the results of ophthalmological, hematological, or serum biochemical examinations. Urinalysis indicated very slight occult blood in 1 female of the high-dose (300 mg/kg) group at the end of the administration period, but it was considered to be unrelated to the administration.

Pathological examinations showed dose-associated reductions in the relative weight of the kidneys in females, but these changes were considered to be unrelated to the administration because individual values were not abnormal. Necropsy revealed no abnormalities. During histological examination, fatty deposition of centrilobular hepatocytes and cell infiltration of portal areas was observed by the light microscopy, and an increase in hepatocellular fat droplets was noted by electron microscopy in the 300 mg/kg group.

In this group, also, increased fat deposition was noted relatively frequently in the kidneys. Other findings, which were considered to be unrelated to the administration, included congestion and megakaryocytic proliferation in the spleen, regional atelectasis and localised lesions of pneumonia in the lungs, leukocytic infiltration around the intrapulmonary bronchi, microfollicular formation of the thyroid glands and reduced stainability (degeneration) of Purkinje cells.

From these findings, the no-effect dose of clarithromycin in a 4-week subacute oral toxicity and a 4-week recovery study in juvenile beagles was considered to be 100 mg/kg for both males and females. The toxic dose was considered to be above 300 mg/kg.

17 SUPPORTING PRODUCT MONOGRAPHS

1. BIAXIN BID (Clarithromycin Tablets, 250 mg & 500 mg), BIAXIN XL (Clarithromycin Extended-Release Tablets, 500 mg) and BIAXIN (Clarithromycin for Oral Suspension, 125 mg / 5 mL & 250 mg / 5 mL), submission control 218738, Product Monograph, BGP Pharma ULC. (OCT 25, 2018)
2. BIAXIN BID (Clarithromycin Tablets, 250 mg & 500 mg) and BIAXIN (Clarithromycin for Oral Suspension, 125 mg / 5 mL & 250 mg / 5 mL), submission control 253289, Product Monograph, BGP Pharma ULC. (OCT 25, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTARO-CLARITHROMYCIN

Clarithromycin for Oral Suspension, USP

Read this carefully before you start taking **TARO-CLARITHROMYCIN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TARO-CLARITHROMYCIN**.

Serious Warnings and Precautions

- TARO-CLARITHROMYCIN should not be used in pregnancy, especially during the first 3 months. If there are no other medicines you can take for your infection, your healthcare professional may give you TARO-CLARITHROMYCIN. If this happens, they will discuss the risks to your baby with you. Talk to your healthcare professional before taking TARO-CLARITHROMYCIN if you are pregnant or think you might be pregnant.
- Taking TARO-CLARITHROMYCIN along with certain other drugs may lead to serious safety issues. Talk to your healthcare professional about all the medicines you take.

What is TARO-CLARITHROMYCIN used for?

- TARO-CLARITHROMYCIN is used to treat certain infections like pneumonia (lung infection), middle ear infections, and infections of the skin and throat that are caused by bacteria.
- It is used to treat mycobacterial infections. Mycobacteria are a group of bacteria that cause several diseases.

Antibacterial drugs like TARO-CLARITHROMYCIN treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, TARO-CLARITHROMYCIN should be taken exactly as directed. Misuse or overuse of TARO-CLARITHROMYCIN could lead to the growth of bacteria that will not be killed by TARO-CLARITHROMYCIN (resistance). This means that TARO-CLARITHROMYCIN may not work for you in the future. Do not share your medicine.

How does TARO-CLARITHROMYCIN work?

TARO-CLARITHROMYCIN is an antibiotic that kills bacteria in your body.

What are the ingredients in TARO-CLARITHROMYCIN?

Medicinal ingredients: Clarithromycin.

Non-medicinal ingredients: Acetone, alginic acid, aspartame, castor oil, citric acid (anhydrous), colloidal silicon dioxide, croscarmellose sodium, flavour peppermint, flavour tutti frutti, hydroxypropyl cellulose, hypromellose, hypromellose phthalate, maltodextrin, povidone, sodium benzoate, sodium chloride, sodium citrate (dihydrate), sucrose, titanium dioxide and xanthan gum.

TARO-CLARITHROMYCIN comes in the following dosage forms:

125 mg / 5mL and 250 mg / 5mL granules for oral suspension (provided in liquid form by your pharmacist).

Do not use TARO-CLARITHROMYCIN if:

- You / your child are allergic to clarithromycin or any of the other ingredients in TARO-CLARITHROMYCIN.
- You / your child are allergic to another medicine called erythromycin or any other medicines from a class of antibiotics called macrolides (such as azithromycin or telithromycin).
- You / your child are taking any of the following medications:
    - Ergotamine, dihydroergotamine (for migraine); Lovastatin, simvastatin, lomitapide (for high cholesterol); Ticagrelor (for cardiovascular disease); Saquinavir (treatment for HIV); Oral midazolam (for trouble sleeping or agitation); Pimozide (for schizophrenia); Colchicine (for gout); Domperidone (for gastrointestinal disorders).
    - Pimozide, ergotamine, dihydroergotamine and colchicine can interact with TARO-CLARITHROMYCIN, possibly leading to an irregular heartbeat. Deaths have occurred.
- You / your child had liver problems after taking TARO-CLARITHROMYCIN, or any other medicine containing clarithromycin, in the past.
- You / your child have severe liver failure in combination with kidney problems.
- You / your child have a history of heart disturbance or irregular heartbeat such as arrhythmias, QT prolongation or torsades de pointes.
- You/ your child have low levels of potassium in the blood (hypokalemia) or low levels of magnesium in the blood (hypomagnesemia).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TARO-CLARITHROMYCIN. Talk about any health conditions or problems you may have, including if you:

- Or your child has now or has had health problems in the past.
- Or your child has or develops severe diarrhea as this may be a sign of a more serious condition.
- Or your child has kidney problems.
- Or your child has liver problems.
- Or your child are taking medicines called digoxin (for heart failure); atorvastatin or pravastatin (for high cholesterol); or midazolam (a sedative).
- Or your child are taking a medicine called quetiapine (for schizophrenia, bipolar depression). Serious and life- threatening side effects have occurred in people taking clarithromycin and quetiapine, including malignant neuroleptic syndrome (fever, rigid muscles, dizziness, fainting, and altered mental state). Your healthcare professional will decide if you/ your child should take this medication.
- Or your child are allergic to other medicines, foods, dyes, or preservatives.
- Or your child have hereditary problems of fructose intolerance, glucose/galactose malabsorption or sucrose/maltase insufficiency since this product contains sucrose.
- Or your child have a condition called phenylketonuria, as TARO-CLARITHROMYCIN contains aspartame.
- Are pregnant, trying to get pregnant or think you might be pregnant.
- Are breastfeeding or planning to breastfeed. Clarithromycin can pass into your

breastmilk and harm your baby.

- Or your child have a condition called myasthenia gravis which is a chronic disease that causes muscle weakness. TARO-CLARITHROMYCIN may make your myasthenia gravis worse.
- Or your child are taking TARO-CLARITHROMYCIN and oral medicines for diabetes (such as gliclazide, glyburide) and / or with insulin as this can result in serious low blood sugar levels (hypoglycemia). Discuss with your healthcare professional how you should monitor your blood sugar levels.
- Or your child are taking warfarin, as there is a risk of serious bleeding with TARO-CLARITHROMYCIN.
- Or your child are taking triazolam, alprazolam or other benzodiazepines (midazolam). These should be used cautiously with TARO-CLARITHROMYCIN due to the serious risk of effects on your brain and spinal cord.
- Or your child are taking TARO-CLARITHROMYCIN and medicines used to prevent blood clots such as dabigatran,rivaroxaban and apixaban, particularly if your healthcare professional has told you that you/ your child are at high risk of bleeding.

Other warnings you should know about:

Serious heart problems:
Use of antibiotics like TARO-CLARITHROMYCIN have resulted in heart problems such as irregular heartbeat, torsades de pointes and QT prolongation sometimes leading to death. Talk to your healthcare professional if you are elderly, have risk factors, or you / your child:

- Have heart disease, heart problems or slow heartbeat.
- Are taking other medicines which are known to cause serious disturbances in heart rhythm.
- Have disturbances in the levels of salts (electrolytes) in your blood, such as low levels of magnesium (hypomagnesemia).

Antibiotic resistance and HIV:
Development of antibiotic resistance (where the medicine no longer works to kill bacteria) has been seen in patients with HIV taking clarithromycin. To avoid this, you should always take your medicine as advised by your healthcare professional.

Driving and using machines:
If you feel dizzy, confused or disorientated while taking TARO-CLARITHROMYCIN, do not drive or operate machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TARO-CLARITHROMYCIN:

- Alfentanil (used during surgery).
- Alprazolam, hexobarbital, phenobarbital, midazolam, triazolam (sedative medications).
- Amlodipine, diltiazem, verapamil (calcium channel blockers often used for high blood pressure).
- Aripiprazole, pimozide, quetiapine, risperidone (for schizophrenia, bipolar depression).
- Atazanavir, indinavir, ritonavir, saquinavir, nevirapine, efavirenz, etravirine, zidovudine (treatments for HIV).

- Atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, lomitapide (for high cholesterol).
- Bromocriptine (used for problems with your pituitary gland and Parkinson's disease).
- Carbamazepine (for seizures, nerve pain or bipolar depression).
- Cilostazol, digoxin, quinidine, disopyramide, warfarin/acenocoumarol, ticagrelor (diseases of your blood vessels and heart).
- Colchicine (treatment for gout).
- Cyclosporine (used for psoriasis, rheumatoid arthritis and after organ transplant).
- Domperidone (used for gastrointestinal disorders).
- Ergotamine, dihydroergotamine (often used for migraine headaches).
- Fluconazole, itraconazole (for fungal infections).
- Insulin, nateglinide, pioglitazone, repaglinide, rosiglitazone (for diabetes).
- Lansoprazole, omeprazole (proton pump inhibitors for heart burn and reflux).
- Methylprednisolone (an anti-inflammatory).
- Phenytoin, valproic acid (treatment of seizures and epilepsy).
- Rifabutin, rifampin (treatments for infections).
- Rivaroxaban, apixaban (to prevent blood clots).
- Sildenafil, tadalafil, vardenafil (treatments for erectile dysfunction).
- St. John's Wort (for depression).
- Tacrolimus (used after organ transplant).
- Theophylline (asthma and other lung problems).
- Tolterodine (treatment for overactive bladder).
- Vinblastine, ibrutinib (cancer treatment).

How to take TARO-CLARITHROMYCIN:

- Always take it exactly how your / your child's healthcare professional has told you.
- Your / your child's healthcare professional will tell you how much TARO-CLARITHROMYCIN to take and when to take it.
- How much you / your child are prescribed will depend on the condition you / your child have.
- You / your child can take TARO-CLARITHROMYCIN with or without meals.
- TARO-CLARITHROMYCIN will be prepared in liquid form by your pharmacist.
- Shake prior to each use to ensure resuspension.

Usual dose:

TARO-CLARITHROMYCIN may be taken with or without meals. TARO-CLARITHROMYCIN sometimes has a bitter after taste, therefore, the suspension should be taken with food and/or juice.

The recommended daily dose of TARO-CLARITHROMYCIN is 15 mg / kg / day, in divided doses every 12 hours. The daily dose should not to exceed 1000 mg. The usual duration of treatment is for 5 to 10 days.

Overdose:

Symptoms of TARO-CLARITHROMYCIN overdose are abdominal pain, vomiting, nausea and diarrhea.

If you think you, or a person you are caring for, have taken too much TARO-CLARITHROMYCIN, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you / your child miss a dose, take / give it as soon as you remember.
- If it is almost time for your / your child's next dose, the missed dose should not be taken.
- Take / give to your child the next dose when you would normally take / give it.
- Never take / give to your child a double dose to make up for a missed dose.

What are possible side effects from using TARO-CLARITHROMYCIN?

These are not all the possible side effects you may have when taking TARO-CLARITHROMYCIN. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- abdominal pain
- abnormal taste
- diarrhea
- ear disorder (trouble hearing and ringing in your ears)
- flatulence
- indigestion
- headache
- nausea
- rash
- vomiting

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Allergic reactions: itching, hives, rash, sore throat, fever, swelling, difficulty breathing, lightheadedness/dizziness, swelling of your tongue or throat, warm red skin or wheezing.			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Clostridium difficile colitis (bowel inflammation): severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness.		✓	
Irregular heartbeat			✓
Myasthenia gravis: muscle weakness, drooping eyelid, vision changes, difficulty chewing and swallowing, trouble breathing.			✓
Hepatitis (liver inflammation): abdominal pain, nausea, vomiting, yellowing of skin and eyes, dark urine.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep TARO-CLARITHROMYCIN and all other medicines out of reach and sight of children.

Store dry powder at controlled room temperature 15° C to 30° C. Protect from light. Store reconstituted product between 15° C and 25° C and use within 14 days. Do not refrigerate. Discard after 14 days. The graduated syringe used for dosage administration should be rinsed between uses. Do not leave syringe in bottle. Do not store reconstituted suspension in syringe.

If you want more information about TARO-CLARITHROMYCIN:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or Taro Pharmaceuticals Inc. at 1-800-268-1975.

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