PRODUCT MONOGRAPH
Including Patient Medication Information

Pr SANDOZ CLARITHROMYCIN XL

Clarithromycin Extended-Release Tablets
500 mg
Ph. Eur.

Antibiotic

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Extended-Release Tablets/ 500 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Sandoz Clarithromycin XL (clarithromycin extended-release tablets) may be indicated in the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Upper Respiratory Tract
Acute maxillary sinusitis due to *Hæmophilus influenzæ, Moraxella catarrhalis,* or *Streptococcus pneumoniæ.*

Lower Respiratory Tract
Acute bacterial exacerbation of chronic bronchitis due to *Hæmophilus parainfluenzæ, Hæmophilus influenzæ, Moraxella catarrhalis, Staphylococcus aureus,* or *Streptococcus pneumoniæ.*

Community-acquired pneumonia due to *Hæmophilus influenzæ, Hæmophilus parainfluenzæ, Moraxella catarrhalis, Streptococcus pneumoniæ, Chlamydia pneumoniæ* (TWAR), or *Mycoplasma pneumoniæ*. See **WARNINGS AND PRECAUTIONS, Susceptibility/Resistance**.

The efficacy and safety of clarithromycin extended-release tablets in treating other infections for which clarithromycin film-coated tablets are approved have not been established.

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

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

CONTRAINDICATIONS

Sandoz Clarithromycin XL is contraindicated in:

- patients with a known hypersensitivity to clarithromycin, erythromycin, other macrolide antibacterial agents or to any ingredient in this product. See **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 **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; WARNINGS AND PRECAUTIONS, Renal; DOSAGE AND ADMINISTRATION, Dosing Considerations and 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 **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS, Drug-Drug Interactions.**

- patients with hypokalaemia due to the risk of prolongation of QT-time 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 **DRUG INTERACTIONS, Drug-Drug Interactions, Table 2**).

- 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 **DRUG INTERACTIONS, Drug-Drug Interactions, Table 2**.

- concomitant therapy with ergot alkaloids (e.g., ergotamine or dihydroergotamine) as this may result in ergot toxicity. See **DRUG INTERACTIONS, Drug-Drug Interactions, Table 2.**

- concomitant administration with **oral** midazolam. See **DRUG INTERACTIONS, Drug-Drug Interactions, Table 2.**

- 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 **DRUG INTERACTIONS, Drug-Drug Interactions, Table 2**.

- concomitant therapy with ticagrelor or ranolazine*.

  * Not marketed in Canada.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- 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 **WARNINGS AND PRECAUTIONS, Special Populations, 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 **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS, Overview**.

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 **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.

Myasthenia Gravis

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

Use of Clarithromycin with Other Drugs
Use of clarithromycin with other drugs may lead to drug-drug interactions.

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 **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 **DRUG INTERACTIONS, Drug-Drug Interactions, Table 2**.

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 **DRUG INTERACTIONS, Drug-Drug Interactions, Table 2**.

HMG-CoA Reductase Inhibitors
Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated. See **CONTRAINDICATIONS**. Caution should be exercised when prescribing clarithromycin with other 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 **DRUG INTERACTIONS, Drug-Drug Interactions, Table 2**.

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 **DRUG INTERACTIONS, Drug-Drug Interactions, Table 2.**

Concomitant administration with oral midazolam is contraindicated. See **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 **DRUG INTERACTIONS, Drug-Drug Interactions, Table 2**.

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class. See **DRUG INTERACTIONS, Drug-Drug Interactions, Table 2**.

Other Drugs
For other established or potential drug-drug interactions and their mechanisms, see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Drug-Drug Interactions**.

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

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.

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 **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, electrolyte disturbances such as hypomagnesemia, 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 **DRUG INTERACTIONS**.

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

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.

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 **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 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 **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment.**

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

Susceptibility/Resistance

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

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 Sandoz Clarithromycin XL 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.

Special Populations

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. See **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions.**

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 **TOXICOLOGY, Reproduction and Teratology.**

Nursing Women: The safety of clarithromycin for use during breast feeding of infants has not been established. Clarithromycin is excreted in human milk.
Preweaned rats, exposed indirectly *via* consumption of milk from dams treated with 150 mg/kg/day for 3 weeks, were not adversely affected, despite data indicating higher drug levels in milk than in plasma.

Pediatrics (6 months to 12 years of age): Use of clarithromycin extended-release tablets in children under 12 years of age has not been studied.

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.

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The majority of side effects observed in clinical trials involving 3563 patients treated with clarithromycin were of a mild and transient nature. The most frequently reported events in adults taking clarithromycin extended-release tablets were diarrhea, abnormal taste and nausea.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials 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 is useful for identifying drug-related adverse events and for approximating rates.

Clarithromycin Extended-Release Tablet

Fewer than 2% of adult patients taking clarithromycin extended-release tablets discontinued therapy because of drug-related side effects. The most frequently reported adverse events in adults taking clarithromycin extended-release tablets were diarrhea (6%), abnormal taste (7%), and nausea (3%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, less than 1% were described as severe.

There have been rare reports of clarithromycin extended-release tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g., suspension) or another antibiotic.

Less Common Clinical Trial Adverse Drug Reactions (<1%) for clarithromycin extended-release tablet

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

Gastrointestinal Disorders:	gastrooesophageal reflux disease and proctalgia
Infections and Infestations:	gastroenteritis
Musculoskeletal and Connective Tissue Disorders:	myalgia
Respiratory, Thoracic and Mediastinal Disorders:	epistaxis

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 1
Post-Market Adverse Drug Reactions

System Organ Class	Adverse Event
Blood and lymphatic system disorders	Agranulocytosis, leukopenia, thrombocytopenia

Table 1 **Post-Market Adverse Drug Reactions**	
System Organ Class	**Adverse Event**
Cardiac disorders[1]	Atrial fibrillation, cardiac arrest, electrocardiogram QT prolonged, extrasystoles, palpitations, Torsades de pointes, ventricular fibrillation, ventricular tachycardia
Ear and labyrinth disorders	Deafness, hearing impaired, hearing loss[2], tinnitus, vertigo
Gastrointestinal disorders	Abdominal pain, constipation, dry mouth, dyspepsia, eructation, esophagitis, flatulence, gastritis, glossitis, pancreatitis, stomatitis, tongue discolouration, tooth discolouration, vomiting
General disorders and administration site conditions	Asthenia
Hepatobiliary disorders	Hepatic failure[3], hepatitis, hepatitis cholestatic, jaundice (cholestatic and hepatocellular)
Immune system disorders	Angioedema, anaphylactic reaction, anaphylactoid reaction, anaphylaxis, hypersensitivity, myasthenia gravis
Infections and infestations	Candidiasis, cellulitis, pseudomembranous colitis, vaginal infection
Investigations	Albumin globulin ratio abnormal, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, blood urea increased, international normalized ratio (INR) increased[4], liver enzymes increased, liver function test abnormal, prothrombin time prolonged[4], urine color abnormal[5]
Metabolism and nutrition disorders	Anorexia, decreased appetite
Musculoskeletal and connective tissue disorders	Musculoskeletal stiffness, myalgia, myopathy, rhabdomyolysis[6]
Nervous system disorders	Ageusia, alteration of sense of smell, anosmia, convulsions, dizziness, dysgeusia, dyskinesia, headache, loss of consciousness, paraesthesia, parosmia, tremor, somnolence
Psychiatric disorders	Abnormal dreams, anxiety, confusion, depersonalization, depression, disorientation, hallucination, insomnia, mania, psychosis
Renal and urinary disorders	Interstitial nephritis, renal failure
Respiratory, thoracic and mediastinal disorders	Asthma, pulmonary embolism
Skin and subcutaneous tissue disorders	Severe cutaneous adverse reactions (SCAR) (e.g., acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS)), acne, dermatitis bullous, Henoch-Schonlein purpura, hyperhidrosis, pruritus, rash, urticaria
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 rhabdomyolosis (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**.

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 **CONTRAINDICATIONS** and **DRUG INTERACTIONS, 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.

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 coadministering 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.

With certain drugs, co-administration of clarithromycin is contraindicated or should be avoided (see **Table 2**).

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.

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 2. The drugs listed in this table are based on drug interactions case reports, clinical trials, or potential interactions due to the expected mechanism of the interaction.

Table 2:
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 torsades de pointes. See **CONTRAINDICATIONS**.

Table 2: **Established or Potential Drug-Drug Interactions with Clarithromycin**			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
			In a study involving 14 healthy volunteers, the concomitant administration of clarithromycin film-coated tablets 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 2: **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 **CONTRAINDICATIONS**.
Colchicine	C	Potential colchicine toxicity	Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (P-gp). Clarithromycin and other macrolides are known to inhibit CYP3A and P-gp. 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 **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 film-coated tablets 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 film-coated tablets 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

Table 2: **Established or Potential Drug-Drug Interactions with Clarithromycin**			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
			clarithromycin simultaneously.
Disopyramide/Quinidine	C	↑ levels of disopyramide, resulting in ventricular fibrillation & QT prolongation (rarely reported) Torsades de pointes	Increased disopyramide plasma levels, resulting in ventricular fibrillation and QT prolongation, coincident with the co-administration of disopyramide and clarithromycin have rarely been reported. 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 **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 **CONTRAINDICATIONS**.
Etravirine	CT	↓ clarithromycin ↑ 14-OH-clarithromycin	Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased.
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-

Table 2: **Established or Potential Drug-Drug Interactions with Clarithromycin**			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
			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 **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 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.
Atorvastatin Rosuvastatin	C		
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}	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.,

Table 2: **Established or Potential Drug-Drug Interactions with Clarithromycin**			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
		↑ levels of clarithromycin	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.
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.**
<u>Oral Hypoglycemic Agents</u> (e.g. insulin)	C P	Hypoglycemia	The concomitant use of clarithromycin and oral hypoglycaemic agents (such as sulphonylurias) 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. Coadministration 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.

Table 2: **Established or Potential Drug-Drug Interactions with Clarithromycin**			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
			Clarithromycin levels decrease when co-administered with rifabutin.
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%)].

Table 2: **Established or Potential Drug-Drug Interactions with Clarithromycin**			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
			QTc prolongation has been reported in patients taking saquinavir along with ritonavir and also in patients taking clarithromycin. Concurent administration of saquinavir and clarithromycin is contraindicated (see **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.
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.
Triazolobenzodiazepines (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 is contraindicated. See **CONTRAINDICATIONS**. If intravenous midazolam is coadministered with clarithromycin, the patient must be closely monitored to allow dose adjustment of midazolam. A drug-drug interaction study between oromucosal midazolam and clarithromycin has not been conducted. 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.

Table 2: **Established or Potential Drug-Drug Interactions with Clarithromycin**			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
			Monitoring the patient for increased CNS pharmacological effects is suggested.
Zidovudine	C	Potential ↓ in zidovudine concentrations	Simultaneous oral administration of clarithromycin film-coated tablets 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.
Other drugs metabolized by CYP3A (e.g., alfentanil, bromocriptine, cilostazol, methylpredni-solone, 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, ibrutinib, 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.

Table 2: Established or Potential Drug-Drug Interactions with Clarithromycin			
Concomitant Medication	**Ref**	**Effect**	**Clinical Comments**
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 DRUG INTERACTIONS.

Drug-Food Interactions
Sandoz Clarithromycin XL must be taken with food.

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.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Effects on Ability to Drive and Use Machines
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.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Sandoz Clarithromycin XL tablets must be taken with food.

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 **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment.**

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

Recommended Dose and Dosage Adjustment
Adults with Respiratory Tract Infection
The adult dosage is 2 x 500 mg tablets (1000 mg) every 24 hours for 5, 7 or 14 days. Sandoz Clarithromycin XL tablets must be taken with food. **Sandoz Clarithromycin XL tablets**

should be swallowed whole and not chewed, broken or crushed. Table 3 provides dosage guidelines.

Table 3: **Dosage Guidelines**		
Infection	**Dosage (Once Daily)**	**Duration (days)**
Acute maxillary sinusitis	1000 mg	14
Acute bacterial exacerbation of chronic bronchitis	1000 mg	5 or 7
Community-acquired pneumonia	1000 mg	7

Renal Impairment
Based on a study done with clarithromycin film-coated tablet, patients with severe renal impairment (creatinine clearance <30 mL/min) have greater clarithromycin exposure than patients with normal renal function (creatinine clearance ≥ 80 mL/min). Clarithromycin C_{max} was about 3.3 times higher and AUC was about 4.2 times higher in the patients with severe renal impairment. The maximum daily clarithromycin dose for patients with severe renal impairment is 500 mg. The safety and efficacy of 500 mg clarithromycin in patients with severe renal impairment has not been established.

In the same study, patients with moderate renal impairment (creatinine clearance 30 to 79 mL/min) had greater clarithromycin exposure than patients with normal renal function, but the elevations were much less than those observed in severe renal impairment. Compared to the subjects with normal renal function, the clarithromycin C_{max} was about 52% higher and the AUC was about 74% higher in the patients with moderate renal impairment. No clarithromycin dose adjustment is required for patients with moderate renal impairment.

Hepatic Impairment
Based on studies done with clarithromycin film-coated tablet, no adjustment of dosage is necessary for subjects with moderate or severe hepatic impairment but with normal renal function. In patients with a combination of hepatic (mild to moderate) and renal impairments, decreased dosage of clarithromycin or prolonged dosing intervals might be appropriate.

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

Missed Dose
If a dose of Sandoz Clarithromycin XL 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.

Administration
Sandoz Clarithromycin XL tablets must be taken with food. The tablets should be swallowed whole and not chewed, broken or crushed.

OVERDOSAGE

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

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

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

General

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

Pharmacokinetics

Clarithromycin Extended-Release Tablets

A summary of clarithromycin pharmacokinetic parameters following the administration of clarithromycin extended-release tablets is provided in Table 4**.** See **DETAILED PHARMACOLOGY, Pharmacokinetics.**

Table 4:
Clarithromycin Pharmacokinetic Parameters following the Administration of Clarithromycin Extended-Release Tablets

	Cmax (mg/L)	**Tmax** (hr)	**AUC0-t** (mg·hr/L)
2 × 500 mg once daily Mean* (fasting conditions)	2.21	5.5	33.72
2 × 500 mg once daily Mean* (fed conditions)	3.77	5.6	48.09

* from **Table 19**

Absorption: Clarithromycin extended-release tablets provided extended absorption of clarithromycin from the gastrointestinal tract after oral administration. Relative to an equal dose of immediate-release clarithromycin film-coated tablets, clarithromycin extended-release tablets provide lower and later steady-state peak plasma concentrations, but equivalent 24-hour AUCs for both clarithromycin and its microbiologically-active metabolite, 14-OH-clarithromycin.

While the extent of formation of 14-OH-clarithromycin following administration of clarithromycin extended-release tablets (2 x 500 mg once daily) under steady-state conditions is not affected by food, administration under fasting conditions is associated with approximately 30% lower clarithromycin AUC relative to administration with food. Similarly, single-dose administration of clarithromycin extended-release (500 mg once daily) is associated with a 25% lower clarithromycin AUC relative to administration of clarithromycin immediate-release film-coated tablets (250 mg twice daily). Therefore, it is recommended that clarithromycin extended-release tablets be given with food.

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

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 5.

Table 5:
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.

Excretion: 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

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 **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic** and **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 **WARNINGS AND PRECAUTIONS, Renal** and **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment.**

STORAGE AND STABILITY

Sandoz Clarithromycin XL should be stored between 15 and 30ºC in well closed containers, protected from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

Sandoz Clarithromycin XL

Oval, light-ochre yellow, biconvex, film-coated tablet, debossed “500” on one side and “CLX” on the other.

Composition

Sandoz Clarithromycin XL contains the following ingredients: clarithromycin, calcium stearate, silicon colloidal anhydrous, hydroxypropyl cellulose, hydroxypropylmethylcellulose, macrogol 400, microcrystalline cellulose, ferric oxide, glycerol dibehenate, polyethylene glycol, polysorbate, povidone, stearic acid, talc, titanium dioxide and vanilla flavour.

Packaging

Sandoz Clarithromycin XL is available in Al/Al blister packs of 10 and 14 tablets and bottles of 50 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

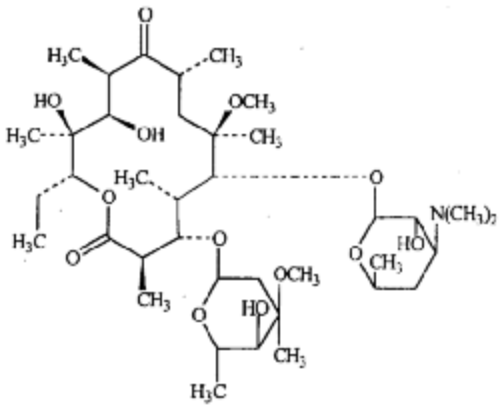
Proper Name: Clarithromycin

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: $C_{38}H_{69}NO_{13}$

Molecular Mass: 747.95 g/mol

Structural Formula:



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

The pKa of clarithromycin is 8.48; the pH of a 0.2% (Methanol: Water, 5:95) slurry is 8.8.

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 coefficient varies from 5.63 to 46.0 for pH water increases from 2 to 8. The melting point of clarithromycin is approximately 225ºC.

CLINICAL TRIALS

Comparative Bioavailability Studies

Single dose crossover comparative bioavailability study of Sandoz Clarithromycin XL 500 mg extended-release tablets in 46 healthy male volunteers (18 to 43 years old) was conducted under fasted conditions. Bioavailability data were measured and the results are summarized in Table 6.

Table 6

Clarithromycin (1 x 500 mg Clarithromycin Extended-Release Tablets) From measured data uncorrected for potency Least-Squares Mean Arithmetic Mean (CV %)				
Parameter	Test Sandoz Clarithromycin XL* 500 mg Extended-Release Tablet	Reference Biaxin® XL† 500 mg Extended-Release Tablet	% Ratio of Least-Square Means	90 % Confidence Interval
AUC_T (ng.h/mL)	9921.0 10972.3 (42.2)	9892.0 10624.4 (38.3)	100.29	91.17–110.32
AUC_∞ (ng.h/mL)	10477.2 11518.6 (40.8)	10482.1 11201.0 (36.7)	99.95	90.67–110.18
C_{MAX} (ng/mL)	539.7 590.0 (41.4)	575.1 612.5 (35.6)	93.84	86.52–101.78
T_{MAX}§ (h)	11.00 (3.00–24.00)	7.50 (2.00–14.00)	---	---
$T_{½}$‡ (h)	6.41 (29.6)	6.57 (33.9)	---	---

* Clarithromycin 500 mg extend-release tablet manufactured for Sandoz Canada Inc.
† Biaxin® XL is manufactured by Abbott Laboratories Limited, Canada, and was purchased in Canada.
§ expressed as the median (range) only.
‡ expressed as the arithmetic mean (CV%) only.

Single dose crossover comparative bioavailability study of Sandoz Clarithromycin XL 500 mg extended-release tablets in 36 healthy male volunteers (20 to 45 years old) was conducted under fed conditions. Bioavailability data were measured and the results are summarized in Table 7.

Table 7

Clarithromycin (1 x 500 mg Clarithromycin Extended-Release Tablets) From measured data uncorrected for potency Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test Sandoz Clarithromycin XL* 500 mg Extended-Release Tablet	Reference Biaxin® XL† 500 mg Extended-Release Tablet	% Ratio of Geometric Means	90 % Confidence Interval
AUC_T (ng.h/mL)	13990.3 14903.8 (32.6)	13425.4 14616.7 (41.1)	104.21	94.31–115.14
AUC_∞ (ng.h/mL)	14424.3 15324.0 (31.9)	13867.6 15035.9 (40.3)	104.01	94.39–114.62
C_{MAX} (ng/mL)	1427.2 1499.9 (30.9)	1285.5 1396.2 (41.4)	111.02	101.36–121.60
T_{MAX}§ (h)	6.00 (3.00–9.00)	5.00 (3.00–12.00)	---	---
$T_{½}$‡ (h)	5.98 (25.0)	5.70 (17.8)	---	---

*Clarithromycin 500 mg extend-release tablet manufactured for Sandoz Canada Inc.
† Biaxin® XL is manufactured by Abbott Laboratories, Limited Canada, and was purchased in Canada.
§ expressed as the median (range) only.
‡ expressed as the arithmetic mean (CV%) only.

Multiple dose crossover comparative bioavailability study of Sandoz Clarithromycin XL 500 mg extended-release tablets in 30 healthy male volunteers (21 to 44 years old) was conducted under fasted conditions. Bioavailability data were measured and the results are summarized in Table 8.

Table 8

Clarithromycin (1 x 500 mg Clarithromycin Extended-Release Tablets) From measured data uncorrected for potency Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test Sandoz Clarithromycin XL* 500 mg Extended-Release Tablet	Reference Biaxin® XL† 500 mg Extended-Release Tablet	% Ratio of Geometric Means	90 % Confidence Interval
AUC_{tau} (ng·h/mL)	13483.4 14779.6 (44.1)	13380.1 14401.6 (38.1)	100.77	91.62–110.84
C_{max} (ng/mL)	918.9 989.7 (40.4)	936.4 995.3 (35.0)	98.14	88.81–108.45
C_{min} (ng/mL)	186.41 236.18 (77.2)	173.40 225.26 (81.30)	107.50	83.92–137.71
T_{max} [§](h)	6.70 (56.55)	5.50 (42.46)	---	---
FL[#] (%)	119.16 (34.1)	122.36 (37.4)	---	---

*Clarithromycin 500 mg extend-release tablet manufactured for Sandoz Canada Inc.
† Biaxin® XL is manufactured by Abbott Laboratories, Limited Canada, and was purchased in Canada.
§ Expressed as the median (range) only
# Expressed as the arithmetic mean (CV%) only

Pneumonia

The clinical and the bacteriological cure rates for all Clinically and Bacteriologically Evaluable Subjects treated with clarithromycin extended-release (ER) in the Community-Acquired Pneumonia (CAP) pivotal study were 87% and 86%, respectively.

Clinical and bacteriological cure rates with the corresponding confidence intervals for Clinically and Bacteriologically Evaluable Subjects in 2 Studies are presented in Table 10**.**

A summary of the study demographics and trial design is presented in Table 9.

Table 9:
Summary of Demographics and Trial Design

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n=number)	Mean Age (Range)
Pivotal Study: M99-077	Phase III, double-blind, randomized, parallel-group, multicenter	clarithromycin ER tablets 2 x 500 mg q.d. levofloxacin tablets 2 x 250 mg q.d. oral 7 days	299	clarithromycin: 49 (19 to 89 years) levofloxacin: 51.2 (18 to 91 years)
Non-Pivotal Study: M98-927	Phase III, double-blind, randomized, parallel-group, multicenter	clarithromycin IR tablets 1 x 250 mg b.i.d./clarithromycin ER tablets 2 x 500 mg q.d. trovafloxacin mesylate tablets (placed in capsules) 1 x 200 mg q.d. oral 7 days	176	clarithromycin ER: 47.6 (19 to 81 years) clarithromycin IR: 49.1 (18 to 76 years) trovafloxacin : 47.3 (19 to 80 years)

Legend: ER = extended-release; q.d. = once daily

Table 10:
Clinical Cure Rates and Bacteriological Cure Rate at the Test-of-Cure Visit*

	Pivotal Study	Non-Pivotal Study
	Clarithromycin ER n/N (%) [95% CI][a]	Clarithromycin ER n/N (%) [95% CI][a]
Clinical Cure Rate[b]	81/93 (87%) [78.5, 93.2]	52/58 (90%) [78.8, 96.1]
P-value[c]; [95% CI][d]	> 0.999, [-10.0, 8.9]	0.292, [-15.8, 3.6]
Bacteriological Cure Rate[b]	80/93 (86%) [77.3, 92.3]	52/58 (90%) [78.8, 96.1]
P-value[c]; [95% CI][d]	0.831, [-11.2, 8.0][e]	0.728, [-14.5, 6.5][f]

a. Exact binomial confidence interval.
b. Assessment was made after 7 days post-treatment in pivotal study and between 7-28 days posttreatment in non-pivotal study unless the subject was a prior clinical failure.
c. P-value is from Fisher's exact test comparing treatment groups.
d. Binomial confidence interval based on normal approximation.
e. comparator is levofloxacin
f. comparator is trovafloxacin mesylate
* Clinically and Bacteriologically Evaluable Subjects in the CAP Studies
Legend: ER = extended-release

Acute Bacterial Exacerbation of Chronic Bronchitis

5-Day Treatment Regimen

One double-blind, controlled study was conducted to evaluate efficacy and safety of clarithromycin extended-release 1000 mg once daily for 5 days treatment of ABECB, as presented in Table 11.

Table 11:
Summary of Demographics and Trial Design
Efficacy of Clarithromycin ER in Acute Bacterial Exacerbation of Chronic Bronchitis - 5-days Treatment

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n=number)	Mean Age (Range)
472	Phase III, Double-blind , randomized, parallel-group, multicenter	Clarithromycin ER 2 x 500 mg q.d for 5 days Clarithromycin IR 500 mg b.i.d for 7 days Oral	Patients with ABECB (n=485)	Clarithromycin ER 62.1 (18-93) Clarithromycin IR 61.6 (34-88)

Legend: b.i.d. = twice daily; q.d. = once daily; ER = extended-release, IR = immediate-release

The bacteriological cure rate for all Clinically and Bacteriologically Evaluable Subjects treated with clarithromycin ER in the Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB) pivotal study was 87%.

Bacteriological cure rates with the corresponding confidence intervals for Clinically and Bacteriologically Evaluable Subjects are presented in Table 12**.**

Table 12:
Bacteriological Cure Rates at the Test-of-Cure Visit*

	Clarithromycin ER n/N (%)	Clarithromycin IR n/N (%)
Bacteriological Cure Rate[b]	82/94 (87%)	91/102 (89%)
95% CI[a]	[78.8, 93.2]	[81.5, 94.5]
Comparison of Cure Rates		
P-value[c];	p = 0.825	
95% CI for Difference in Cure Rate[d]	[-11.6, 7.6]	

a. Exact binomial confidence interval.
b. Bacteriological assessment was made at Evaluation 4 (between Study Days 14 and 40), unless the subject was a bacteriological failure.
c. P-value is from Fisher's exact test comparing treatment groups.
d. Binomial confidence interval based on normal distribution approximation with a continuity correction
* Clinically and Bacteriologically Evaluable Subjects in the ABECB Study
Legend: ER = extended-release; IR = immediate-release

The clinical cure rates for all Clinically and Bacteriologically Evaluable Subjects treated with clarithromycin ER in the Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB) pivotal study are presented in Table 13**.**

Table 13:
Clinical Cure Rates for Target Pathogens

Pretreatment Target Pathogen	Clarithromycin ER	Clarithromycin IR	p-value
H. influenzæ	34/40 (85%)	34/38 (89%)	0.738
H. parainfluenzæ	23/28 (82%)	39/43 (91%)	0.304
M. catarrhalis	24/26 (92%)	14/18 (78%)	0.208
S. pneumoniæ	14/19 (74%)	15/20 (75%)	>0.999
S. aureus	7/9 (78%)	10/12 (83%)	>0.999

a. p-value from Fisher's exact test comparing treatment groups
Legend: ER = extended-release; IR = immediate-release

Long-term (3 months) recurrence rates of ABECB after 5-day treatment with clarithromycin extended-release tablets has not been investigated in the pivotal trial.

7-Day Treatment Regimen
One double-blind controlled clinical trial was conducted to evaluate the efficacy and safety of clarithromycin 500 mg two tablets once daily for 7 days treatment of ABECB, as presented in Table 14**.**

Table 14:
Summary of Demographics and Trial Design Efficacy of Clarithromycin ER in Acute Bacterial Exacerbation of Chronic Bronchitis - 7 Days treatment

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n=number)	Mean Age (Range)
756	Phase III, Double-blind , randomized, parallel-group, multicenter	Clarithromycin ER 2 x 500 mg q.d for 7 days Clarithromycin IR 500 mg b.i.d for 7 days	Patients with ABECB (n=627)	54.4 years (14 to 89)

Legend: b.i.d. = twice daily; q.d. = once daily; ER = extended-release; IR = immediate-release

The primary efficacy parameters evaluated in Study 756 were the bacteriological cure rates, target pathogen eradication and clinical cure rates. Bacteriological and clinical cure rates with the corresponding confidence intervals for Clinically and Bacteriologically Evaluable Subjects are presented in Table 15.

Table 15:
Bacteriological and Clinical Cure Rates at Test-of-Cure Visit – Study 756

	Clarithromycin ER n/N (%) [95% CI][b]	Clarithromycin IR n/N (%) [95% CI][b]	P-value[a] [95% CI][c]
Bacteriological Cure Rate[d]	85/99*(86%) [77.4, 92.0]	70/82 (85%) [75.8, 92.2]	> 0.999 [-9.8, 10.8]
Clinical Cure Rate	83/100 (83 %) [74.2, 89.8]	67/82 (82%) [71.6, 89.4]	0.847 [-9.9, 12.4]

* One subject with indeterminate bacteriological response was not included in calculating the rate.
a. P-value is from Fisher's exact test comparing treatment groups.
b. Exact binomial confidence interval.
c. Binomial confidence interval based on normal approximation.
d. Assessment was made at Evaluation 3 (7 to 23 days post-treatment) unless the subject was a bacteriological failure before Evaluation 3.
Legend: ER = extended-release; IR = immediate-release

Overall eradication rates and corresponding confidence intervals, as well as target pathogen eradication rates, for clinically and bacteriologically evaluabale subjects are presented in Table 16**.**

Table 16:
Target Pathogen Eradication Rates at Test-of-Cure Visit – Study 756

	Clarithromycin ER n/N (%) [95% CI][b]	Clarithromycin IR n/N (%) [95% CI][b]	P-value[a] [95% CI][c]
Overall Pathogen Eradication Rate[d]	100/116 (86 %) [78.6, 91.9]	86/98 (88%) [79.6, 93.5]	0.840 [-10.6, 7.5]
Eradication Rate[d]			

H. infuenzæ	22/28 (79%)	17/22 (77%)	0.840
M. catarrhalis	22/25* (88%)	25/26* (96%)	[-10.6, 7.5]
S. pneumoniæ	22/25 (88%)	9/11 (82%)	
H. parainfluenzæ	24/26 (92%)	25/28 (89%)	
S. aureus	10/12 (83%)	10/11 (91%)	

* One subject with indeterminate bacteriological response was not included in calculating the rate.
a. P-value is from Fisher's exact test comparing treatment groups.
b. Exact binomial confidence interval.
c. Binomial confidence interval based on normal approximation.
d. Assessment was made at Evaluation 3 (7 to 23 days post-treatment) unless the subject was a bacteriological failure before Evaluation 3.

Comparative Bioavailability Studies

Relative Bioavailability of Clarithromycin Extended-Release Tablet and Clarithromycin Film-Coated Tablet Formulations

Steady-state pharmacokinetic studies compared the new clarithromycin extended-release 500 mg tablet dosage form to the standard 250 mg and 500 mg clarithromycin immediate-release film-coated tablets.

In the first study, the steady-state pharmacokinetics of clarithromycin and 14-OH-clarithromycin were studied in 30 healthy subjects under non-fasting (moderate-fat meal) conditions. The subjects received clarithromycin extended-release tablets (2 × 500 mg once daily) or clarithromycin immediate-release film-coated tablets (500 mg twice daily). The pharmacokinetic and bioavailability parameters for clarithromycin are summarized in Table 17.

Table 17:
Comparative Steady-State Bioavailability Data for Clarithromycin – Three Lots of Clarithromycin 500 mg ER Tablets *versus* Clarithromycin 500 mg IR Tablets Under Non-Fasting (Moderate-Fat Meal) Conditions

	Arithmetic Mean (CV%)			**Relative Bioavailability**		
Parameter	**ER Tablet Regimen A**	**ER Tablet Regimen B**	**ER Tablet Regimen C**	**IR Tablet Regimen D**	**Point Estimate (%)+**	**Confidence Interval***
AUC_τ (mcg·h/mL)	42.2 (30)	44.9 (34)	42.1 (31)	46.1 (30)	A *vs* D: 92.1 B *vs* D: 96.2 C *vs* D: 90.3	85.4-99.4 89.1-103.8 83.7-97.5
C_{max} (mcg/mL)	2.81 (37)	2.78 (34)	2.59 (27)	3.51 (28)	A vs D: 79.2 B *vs* D: 77.2 C *vs* D: 72.9	71.8-87.3 70.0-85.1 66.1-80.4
C_{min} (mcg/mL)	0.83 (41)	0.83 (53)	0.76 (49)	0.91 (43)	A *vs* D: 94.3 B *vs* D: 86.0 C *vs* D: 79.0	75.9-117.3 69.1-106.9 63.5-98.2
T_{max} (hr)	6.5 (61)	5.5 (63)	7.8 (51)	2.1 (28)	--	--
FI (%)	113 (26)	107 (27)	108 (26)	138 (18)	--	--

Regimen A = 2 x 500 mg clarithromycin ER tablet lot 1, every morning for 5 days.
Regimen B = 2 x 500 mg clarithromycin ER tablet lot 2, every morning for 5 days.
Regimen C = 2 x 500 mg clarithromycin ER tablet lot 3, every morning for 5 days.
Regimen D = 1 x 500 mg clarithromycin immediate-release film-coated (IR) tablet, every 12 hours for 5 days.
+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.
* 90% confidence intervals for AUCτ 95% confidence intervals for Cmax and Cmin.
Legend: ER = extended-release; ; FI = Fluctuation Index; IR = immediate-release

The results from this multiple dose study showed that at steady state under non-fasting conditions, all 3 lots of the test extended-release formulation met the requirements for demonstrating bioavailability with respect to AUC_τ. The significantly lower clarithromycin C_{max} values and the longer T_{max} values suggested that the test formulation provided extended release of

clarithromycin *in vivo*. The significantly lower fluctuation index (FI) values indicated that clarithromycin plasma concentrations fluctuated less for the extended-release tablet regimens than for the immediate-release tablet regimen.

In the second study, the steady-state pharmacokinetics of clarithromycin and 14-OH-clarithromycin were studied in 32 healthy subjects under non-fasting (moderate-fat meal) conditions. The subjects received a clarithromycin extended-release 500 mg tablet once daily or clarithromycin 250 mg immediate-release film-coated tablet twice daily.

The pharmacokinetic and bioavailability parameters for clarithromycin are summarized in Table 18.

Table 18:
Comparative Steady-State Bioavailability Data for Clarithromycin – Clarithromycin 500 mg ER Tablets *versus* Clarithromycin 250 mg IR Tablets Under Non-Fasting (Moderate-Fat Meal) Conditions

	Arithmetic Mean (CV %)		**Relative Bioavailability**	
Parameter	**ER Tablet Regimen A**	**IR Tablet Regimen B**	**Point Estimate (%)+**	**Confidence Interval***
AUC_τ (mcg·h/mL)	20.4 (43)	21.0 (33)	94.6	84.8-105.5
C_{max} (mcg/mL)	1.45 (30)	1.94 (35)	75.8	67.7-84.9
C_{min} (mcg/mL)	0.31 (73)	0.34 (45)	75.1	59.2-102.8
T_{max} (hr)	5.6 (38)	2.4 (59)	--	--
FI (%)	148 (36)	184 (22)	--	--

Regimen A = 1 x 500 mg clarithromycin ER tablet, every morning for five days.
Regimen B = 1 x 250 mg clarithromycin immediate-release film-coated (IR) tablet, every 12 hours for 5 days.
+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.
* 90% confidence intervals for AUC_τ; 95% confidence intervals for C_{max} and C_{min}.
Legend: ER = extended-release; FI = Fluctuation Index; IR = immediate-release

The results from this multiple-dose study showed that the extended-release tablet was not significantly different from the 250 mg film-coated tablet in terms of AUC_τ. The significantly lower clarithromycin C_{max} values and longer T_{max} values suggested that the test formulation provided extended release of clarithromycin *in vivo*. The significantly lower FI values indicated that clarithromycin plasma concentrations fluctuated less for the extended-release tablet regimen than for the immediate-release regimen.

*In the third study***,** the steady-state pharmacokinetics of clarithromycin and 14-OH-clarithromycin were studied in 32 healthy subjects. The subjects received clarithromycin extended-release tablets (2 x 500 mg) once daily under fasting or non-fasting (high-fat meal) conditions. The pharmacokinetic and bioavailability parameters for clarithromycin are summarized in Table 19.

Table 19:
Effect of Food on the Steady-State Bioavailability of Clarithromycin – Clarithromycin 500 mg ER Tablets – Fasting *versus* Non-Fasting (High-Fat Meal) Conditions

	Arithmetic Mean (CV %)		Relative Bioavailability	
Parameter	**ER Tablet Fasting Regimen A**	**ER Tablet Non-Fasting Regimen B**	**Point Estimate (%)+**	**Confidence Interval***
AUC_τ (mcg·h/mL)	35.9 (35)	49.2 (21)	70.1	62.4-78.7
C_{max} (mcg/mL)	2.33 (30)	3.91 (27)	58.7	51.4-67.0
C_{min} (mcg/mL)	0.76 (58)	0.80 (48)	95.9	72.0-125.8
T_{max} (hr)	5.5 (57)	5.6 (35)	--	--
FI (%)	113 (40)	153 (29)	--	--

Regimen A = 2 x 500 mg clarithromycin ER tablets under fasting conditions, every morning for 5 days.
Regimen B = 2 x 500 mg clarithromycin ER tablets under nonfasting conditions, every morning for 5 days.
+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.
* 90% confidence intervals for AUC_τ; 95% confidence intervals for C_{max} and C_{min}.
Legend: ER = extended-release; FI = Fluctuation Index

The results from this multiple dose study showed that the clarithromycin C_{max} and AUC_τ central values for the extended-release clarithromycin tablet formulation administered under fasting conditions were approximately 41% and 30% lower, respectively than the central values for the same formulation administered with high-fat meal. The clarithromycin C_{min} values were similar when the extended-release formulation was given under fasting *versus* non-fasting conditions.

DETAILED PHARMACOLOGY

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 Film-Coated Tablets

Pharmacokinetics for clarithromycin and 14-OH-clarithromycin metabolite were first studied following the oral administration of a single dose of 250 mg or 500 mg or multiple doses of clarithromycin 250 mg tablet.

Single Dose

Plasma levels were determined in 20 subjects following oral administration of a single-dose of 250 mg or 500 mg of clarithromycin under fasting conditions. C_{max} occurred at 1.00 and 1.77 (mg/L) and T_{max} were 1.5 and 2.2 hours, respectively for the 250 mg and 500 mg. (See **Table 20, Figures 1 and 2**).

Table 20:
Mean (± SD) Pharmacokinetic Parameters for Clarithromycin Administered as a Single Dose in the Absence of Food

Variable	Clarithromycin Dose	
	250 mg	**500 mg**
Number of male evaluable patients	20	20
C_{max} (mg/L)	1.00 ± 0.34	1.77 ± 0.65
C_{max}/100 mg[1]	0.40	0.35
T_{max} (hr)	1.5 ± 0.8	2.2 ± 0.7
AUC (mg·hr/L)	5.47 ± 1.93[2]	11.66 ± 3.67[3]
AUC/100 mg[1]	2.19	2.33

[1] $C_{max}/100\ mg = C_{max} \times \frac{100\ mg}{dose}$; $AUC/100\ mg = AUC \times \frac{100\ mg}{dose}$

[2] $AUC_{0\text{-}12\ hr}$

[3] $AUC_{0\text{-}14\ hr}$

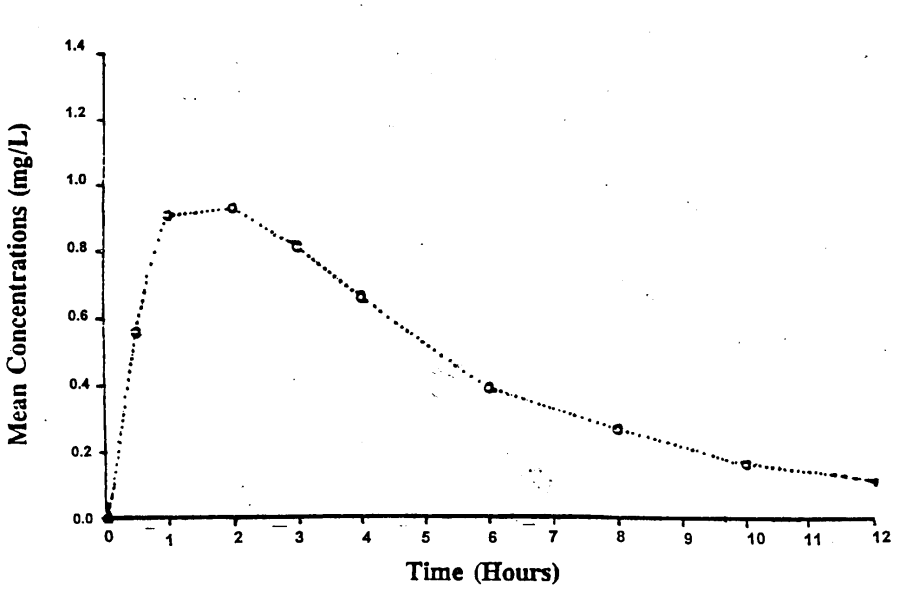


Figure 1: Plasma Clarithromycin Concentration (mg/L) *vs* Time Following Oral Administration of a Single Dose of Clarithromycin 250 mg.

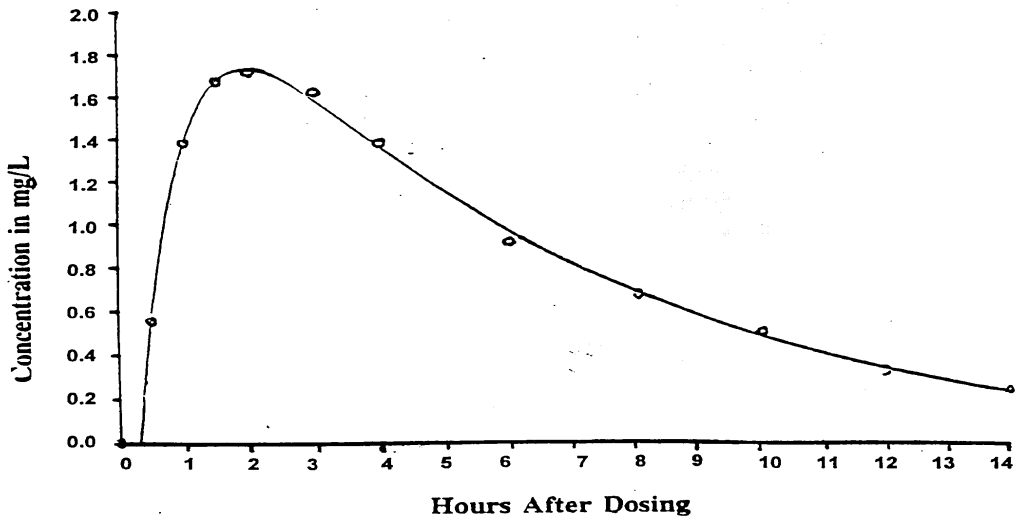


Figure 2: Plasma Clarithromycin Concentration (mg/L) *vs* Time Following Oral Administration of a Single Dose of Clarithromycin 500 mg.

Multiple Dose

Representative estimated pharmacokinetic parameters for clarithromycin and 14-OH-clarithromycin metabolite after a single oral 250 mg dose and after the 5th dose of clarithromycin administered orally at 250 mg twice daily are listed in Table 21.

Table 21:
Representative Estimated Single and Multiple-Dose Pharmacokinetic Parameters for Clarithromycin and 14-OH-Clarithromycin

Variables	Single Dose (250 mg)		Multiple Dose after 5th Dose (250 mg b.i.d.)	
	Clari.	**14-OH**	**Clari.**	**14-OH**
C_{max} (mg/L)	0.74 ± 0.24	0.61 ± 0.17	1.00 ± 0.29	0.63 ± 0.19
$t_{1/2}$(hr)	2.7	4.2	3.5	4.7
AUC_{0-12}(mg·hr/L)	4.27 ± 1.52	4.91 ± 1.12	6.34 ± 1.82	4.72 ± 1.29

Legend: Clari. = clarithromycin; 14-OH = 14-OH-clarithromycin; b.i.d.= twice daily

The pharmacokinetics of clarithromycin and its 14-OH-metabolite indicate that the steady-state concentration is achieved by the 5th dose using 250 mg of clarithromycin twice daily.

The mean plasma concentration-time along the predicted curves for clarithromycin and 14-OH-clarithromycin metabolite are shown in Figure 3.

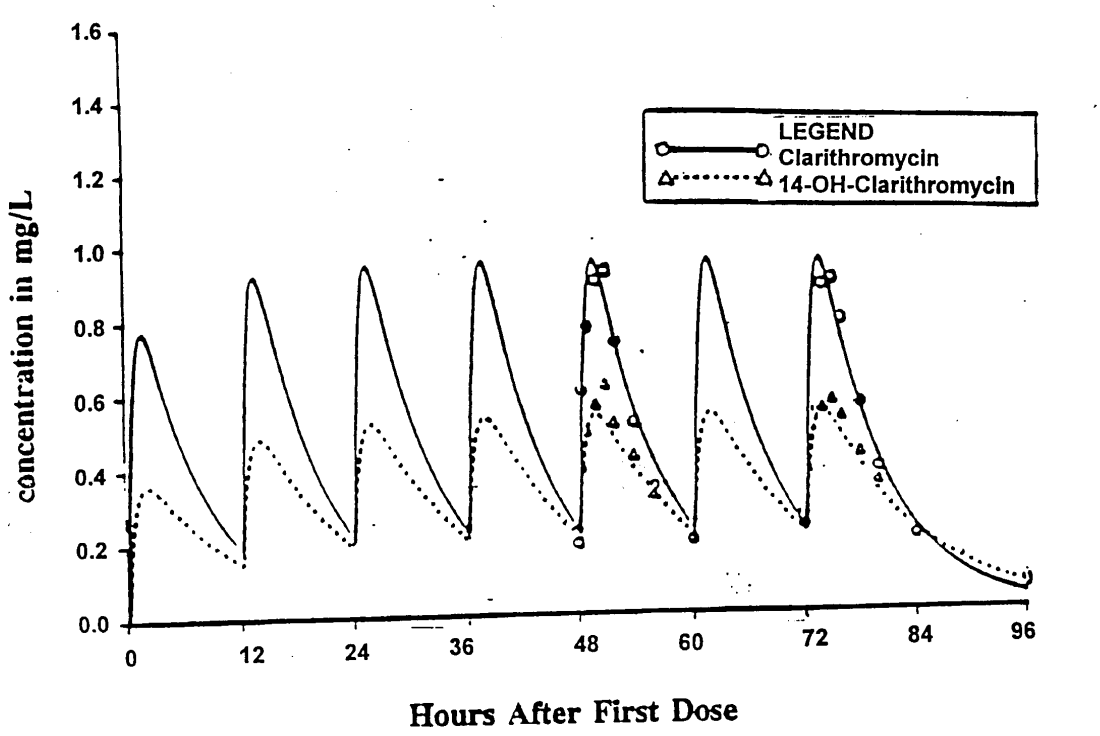


Figure 3: Mean Plasma Concentrations of Clarithromycin and 14-OH-Clarithromycin *vs* Time Following Seven 250 mg B.I.D. Oral Doses of Clarithromycin.

At 250 mg twice daily, approximately 20% of an orally administered dose 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 10-15% 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.

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

The pharmacokinetics of clarithromycin were also altered in subjects with impaired renal function. See **WARNINGS AND PRECAUTIONS, Renal** and **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment.**

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 ærobic and anærobic gram-positive and gram-negative organisms as well as most MAC microorganisms. The *in vitro* activity of clarithromycin is presented in Table 22.

Additionally, the 14-OH-clarithromycin metabolite also has significant antimicrobial activity which may be additive to the activity of the parent compound. Against *Hæmophilus influenzæ*, 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.

The ranges of minimum inhibitory concentrations (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 Tables 23 and 24. 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 enterobacteriaceæ, 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 INDICATIONS AND CLINICAL USE section:

Aerobic Gram-Positive microorganisms	**Aerobic Gram-negative microorganisms**	**Other microorganisms**
Staphylococcus aureus *Streptococcus pneumoniae*	*Haemophilus influenza* *Haemophilus parainfluenzae* *Moraxella catarrhalis*	*Mycoplasma pneumoniae* *Chlamydia pneumoniae (TWAR)*

The following in vitro data are available, but **their clinical significance is unknown.** Clarithromycin exhibits in vitro activity against most strains of the following microorganisms; however, the safety and effectiveness of clarithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials (See **MICROBIOLOGY, Tables 22-24 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 22
***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 pneumoniæ	26	38	84	84	84	100	-	-	-	-	-	-	-
Streptococcus agalactiæ (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 gonorrhoeæ	39	23	35	64	100	-	-	-	-	-	-	-	-
Hæmophilus influenzæ	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 23: *In vitro* Susceptibility of Different Bacteria to Clarithromycin

Microorganisms	Number of strains	MIC (mg/L)		
		Range	50%	90%
Mycoplasma pneumoniæ	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
Hæmophilus influenzæ	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 gonorrhoeæ	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 chelonæ	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 pneumoniæ	49	0.004-0.025	0.016	0.031

Table 24: *In vitro* Susceptibility of Different Bacteria to 14-OH-Clarithromycin

Microorganisms	Numberof strains	MIC (mg/L)		
		Range	50%	90%
Streptococcus pyogenes	15	0.015-0.03	0.015	0.03
Streptococcus pneumoniæ	13	≤0.004-0.015	0.008	0.015
Streptococcus agalactiæ	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 gonorrhoeæ	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
Hæmophilus influenzæ	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
Propionibacterum acnes	12	0.03->128	0.03	0.06

Susceptibility Testing Excluding *Mycobacteria*

Dilution Techniques

Quantitative methods are used to determine antimicrobial 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[21] (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 25**.

Table 25:
Criteria for the Interpretation of Standard Single Disc and Dilution Susceptibility Tests except for *H. influenzæ*

	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[22] and M100-S8[23].

The standard single disc susceptibility test (using the 15 mcg clarithromycin disc) for *H. influenzæ* should be interpreted according to the criteria in **Table 26**.

Table 26:
Criteria for the Interpretation of Standard Single Disc and Dilution Susceptibility Tests for *H. influenzæ*

	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[22] 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 25**.

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. influenzæ* (see **Table 27**).

Table 27: **Standard Clarithromycin Powder** **MIC Values**	
Microorganisms	**MIC (mcg/mL)**
S. aureus ATCC 29213	0.12 to 0.5
H. influenzæ 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. influenzæ* (see **Table 28**).

Table 28: Zone Diameter for the 15 mcg Clarithromycin Disc	
Microorganisms	**Zone Diameter (mm)**
S. aureus ATCC 25923	26 to 32
H. influenzæ 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 oleic acid-albumin-dextrose-catalase (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 *M. avium* complex (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 one 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.

TOXICOLOGY

Acute Toxicity

Clarithromycin Film-Coated Tablets

The acute toxicity of clarithromycin administered by a variety of routes, was studied in mice and rats. The median lethal dose by the oral route ranged from 2.7 to >5.0 g/kg. Acute toxicity did not differ markedly between sexes (see **Table 29**).

Table 29:
Acute LD_{50} values of Clarithromycin

Species	Sex	Route	LD_{50} value (g/kg)
Mice	M	PO	2.74
	F	PO	2.7
	M	SC	>5.0
	F	SC	>5.0
	M	IP	1.03
	F	IP	0.85
	M	IV	0.17
	F	IV	0.2
Rats	M	PO	3.47
	F	PO	2.7
	M	SC	>5.0
	F	SC	>5.0
	M	IP	6.69
	F	IP	7.58

Legend: i.p. = intraperitoneal; i.v. = intravenous; p.o. = oral; s.c. = subcutaneous

The primary signs of toxicity included reduction in activities, behaviors, weight gains, respiration rates and sedation. The emetic activity of clarithromycin prevented the determination of the lethal dose in dog.

The acute oral toxicity of clarithromycin in very young mice and rats was determined. The median lethal dose (1.2 g/kg) was about 2-fold that seen in the older rodents.

Subchronic Toxicity
Clarithromycin Film-Coated Tablets
Studies were conducted in rats, dogs and monkeys with clarithromycin administered orally. The duration of administration ranged from 14 days to 42 days.

Rats
One study in rats (with oral doses up to 800 mg/kg/day) failed to show adverse effects in rats exposed to 50 mg/kg/day for 4 weeks. The clinical signs observed at toxic doses were reduced motility, piloerection, hypothermia and perineal urine staining. Changes occurred in biochemical parameters at 200 and 800 mg/kg/day indicative of hepatotoxicity which was confirmed by histopathologic findings of hepatocyte necrosis.

Other pathologic findings at the top 2 dose levels included swelling of the renal cortical tubular epithelia and atrophic changes to the lymphatic and genital systems. The same toxicity profile was observed in immature rats following the daily administration of oral doses up to 150 mg/kg/day of clarithromycin for 6 weeks. At 150 mg/kg/day, there was an increase in relative weights of liver and kidneys.

Dogs
Dogs were dosed orally with 0, 6.25, 25, 100 or 400 mg/kg/day of clarithromycin daily for 28 days. Emesis occurred sporadically in the treated dogs. No other adverse effects were seen in dogs exposed to 6.25 mg/kg/day. The clinical signs at higher dosages included loose stools, lacrimation and conjunctivitis.

Slight anorexia was noted in dogs receiving 100 mg/kg/day or more. Dogs at 400 mg/kg/day exhibited reduced red blood cell count, hematocrit, hemoglobin concentration, serum albumin, and mean urine pH and specific gravity. Increases were seen in serum transaminase, alkaline phosphatase, and total bilirubin concentrations.

Bilirubin was detected in the urine. Other pathologic changes at 400 mg/kg/day included biliary hyperplasia, gastric glandular atrophy, renal tubule epithelial atrophy, edema of the iris, ciliary body and choroid, capillary proliferation in the cornea, suppression of spermatogenesis, and adrenal medullary degeneration.

Monkeys
Monkeys were treated daily for 1 month with oral doses of 0, 25, 100 or 400 mg/kg/day. Two animals out of 10 receiving 400 mg/kg/day died. Salivation was recorded at all dosage levels. No other adverse effects were seen in animals treated daily with 25 mg/kg/day.

The clinical signs observed at higher doses and most frequently at 400 mg/kg/day were vomiting, emesis, sunken eyes, dehydration, emaciation, low rectal temperature, body weight loss, reduced food consumption, cloudiness of the cornea and reduction in intraocular pressure. Yellow discoloured feces were passed on a few isolated occasions by some animals given a dose of

400 mg/kg/day. As with the other species, the liver was the primary target at toxic doses as shown by early elevation of serum concentration of glucose, BUN, creatinine, ALT, AST, LDH, amylase and/or triglyceride; an electrolyte imbalance and low levels of protein, cholesterol, phospholipid; elevated leucine aminopeptidase (LAP).

Principal histopathologic changes were seen mainly in high-dose monkeys, but some mid-dose monkeys exhibited similar alterations. Changes included necrosis and vacuolation of hepatocytes, vacuolation of renal cortical tubules, no spermatogenesis, thymic regression and single cell necrosis of the stomach. In man the recommended dose is 500 to 1000 mg/day or 7.1-14.3 mg/kg/day (70 kg person).

Chronic Toxicity

Clarithromycin Film-Coated Tablets

Rats (20/sex/group) were treated daily with oral doses of 0, 15, 37.5, 75 or 150 mg/kg/day for three months. There were eight incidental deaths, but none of them were considered treatment related. Clinical signs included increased salivation, dehydration, hyperactivity and were observed in a dose-related manner. The only toxic effect noted was some variation in body weight gain. No toxicologically significant changes occurred in hematology, biochemistry or urinalysis results.

Post mortem, there was an increase in mean relative liver and kidney weights at the top dose level. No microscopic changes were detected in the kidneys, but in the liver, there was a sex/dose-related increase in multinucleated hepatocytes. Effects were only seen in females at 150 mg/kg/day but in males occurred as low as 37.5 mg/kg/day.

A six-month oral study was also performed in rats (20 to 27/sex/group) at dosages of 0, 1 to 6, 8, 40 or 200 mg/kg/day. Seven male and female rats from the control group and the 40 and 200 mg/kg/day groups were allowed a 63 day non-dosed recovery period. No mortalities occurred. Body weight and food intake were reduced at high doses during the dosing phase but normalized during recovery.

Water intake and urine volume increased in males and females of the 40 and 200 mg/kg/day groups. Dose-related hematological changes included reduced erythrocytes and HCT with increased MCV, MCH and MCHC and relative eosinophil counts. Biochemical changes were mainly restricted to the high dose group and included increased ALP and decreased phospholipids; decreased total cholesterol and triglycerides, and increased AST and ALT in males only and decreased albumin in females only.

Organ weight increases were found to include cecum, adrenals, liver, and spleen. Histopathological examinations showed drug-related, recovery-reversible increases in multinucleated hepatocytes associated with minimal and focal necrosis in livers of both sexes at the top two dose levels. No relevant pathology was found in the cecum, adrenals or spleen to account for the increased weights. After recovery only the 200 mg/kg/day group had increased multinucleated hepatocytes.

Dogs (7/sex/group) were administered daily with oral doses of 0, 10, 30, or 100 mg/kg/day of clarithromycin for three months. Emesis occurred at levels of 30 mg/kg and above. One male high dose dog was killed *in extremis* on day 69. Drug-related lesions were seen in the liver, gall bladder, thymus and stomach.

Hematological and biochemical changes at the high dose level included, decreased RBC and HCT, increased ALT, ALP, GGT, and decreased total protein and albumin. No significant organ weight changes were recorded, but treatment-related microscopic alterations in the liver and stomach of mild and high-dose dogs were seen, as well as changes in gall bladder, spleen and thymus of high dose animals.

A six month oral study was performed in dogs (4 to 5/sex/group) at dosages of 0, 0.8, 4, 20 or 100 mg/kg/day. At the 0 and 100 mg/kg levels, one male and one female dog were allowed a one month, non-dosed, recovery period. One male high-dose dog died on day 174. This death was considered to be as a direct result of clarithromycin administration. Histopathologic examination revealed hepatic parenchymal damage, identifying the cause of clinical jaundice. Clinical signs during the dosing phase of the study were restricted to the top two dose levels and included emesis and ocular signs. Food consumption and water intake were reduced at 20 and 100 mg/kg/day.

Hematologic changes at 100 mg/kg were indicative of subclinical anemia. Biochemical alterations at the same level were associated with liver damage. Ocular changes were only apparent at the top dose level.

Increase in the weights of lung, liver, spleen, adrenals and kidneys were found at 100 mg/kg/day. Histopathologic examination of these organs showed degeneration of liver parenchyma, and toxic effects in adrenals. The thymus weight was reduced at 100 mg/kg/day. At the end of the recovery period all findings had regressed or reduced.

Monkeys (5 to 6/sex/group) were similarly administered clarithromycin at levels of 0, 25, 50 or 100 mg/kg/day for six months. At the 0 and 100 mg/kg/day levels, one male and one female monkey were allowed a one-month recovery period. One high-dose female died in week 25. Inhalation of vomit was considered to be the cause of death. Clinical signs were restricted to a dose-related incidence of emesis and salivation. No treatment-related effects were found in food consumption, ophthalmoscopy or hematology. Weight loss was restricted to 1 high-dose female. Minor serum chemistry changes were seen at the 100 mg/kg level, particularly in plasma proteins. Urinalysis revealed a dose-related lowering of pH and SG at 13 weeks only. Organ weight increases in liver, adrenal and kidneys were seen at high doses, but pathology was restricted to minimal liver changes consisting of cytoplasmic rarefaction of centrilobular hepatocytes. All changes were reversed during the recovery period.

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 Teratology
Fertility and reproduction studies have shown that daily doses of 150 to 160 mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after 150 mg/kg/day were 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/sq m, which is 17 times less than the maximum proposed human oral daily dose of 618 mg/sq m.

Special Studies
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.

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PART III: PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Sandoz Clarithromycin XL
Clarithromycin Ph. Eur. 500 mg extended-release tablets

Read this carefully before you start taking Sandoz Clarithromycin XL 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 Sandoz Clarithromycin XL.

Serious Warnings and Precautions

- **Sandoz Clarithromycin XL 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 doctor may give you Sandoz Clarithromycin XL. If this happens, they will discuss the risks to your baby with you. Talk to your doctor before taking Sandoz Clarithromycin XL if you are pregnant or think you might be pregnant.**

- **Taking Sandoz Clarithromycin XL along with certain other drugs may lead to serious safety issues. Talk to your doctor about all the medicines you take.**

What the medication is used for?
Sandoz Clarithromycin XL is used to treat certain infections like pneumonia, bronchitis and infections of the sinuses that are caused by bacteria.

The efficacy and safety of clarithromycin extended-release tablets in treating other infections for which other dosage forms of clarithromycin are approved have not been established.

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

How does Sandoz Clarithromycin XL work?
Sandoz Clarithromycin XL is an antibiotic that kills bacteria in your body.

What are the ingredients in Sandoz Clarithromycin XL?
Medicinal ingredients: Clarithromycin
Non-medicinal ingredients: Calcium stearate, silicon colloidal anhydrous, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, ferric oxide, glycerol dibehenate, polyethylene glycol, polysorbate, povidone, stearic acid, talc, titanium dioxide and vanilla flavour.

Sandoz Clarithromycin XL comes in the following dosage forms:
500 mg extended-release tablets.

Do not use Sandoz Clarithromycin XL if:

- You are allergic to clarithromycin or any of the other ingredients in Sandoz Clarithromycin XL.
- You are allergic to another medicine called erythromycin or any other medicines from a class of antibiotics called macrolides (such as azithromycin or telithromycin).
- You are taking any of the following medications:
    - Ergotamine, dihydroergotamine (for migraine); Lovastatin, simvastatin (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 Sandoz Clarithromycin XL, possibly leading to an irregular heartbeat. Deaths have occurred.
- You had liver problems after taking Sandoz Clarithromycin XL in the past.
- you have severe liver failure in combination with kidney impairment.
- You have a history of heart disturbance or irregular heartbeat such as arrhythmias, QT prolongation or torsades de pointes.
- You have hypokalaemia (low potassium levels in the blood).

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

- Have now or have had health problems in the past.
- Have or develop severe diarrhea as this may be a sign of a more serious condition.
- Have kidney problems;
- have liver problems;
- Are taking medicines called digoxin (for heart failure); atorvastatin or pravastatin (for high cholesterol); or midazolam (a sedative).
- 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 doctor will decide if you should take this medication;
- Are allergic to other medicines, foods, dyes, or preservatives;
- Have a hereditary problem of galactose intolerance, Lapp lactase insufficiency or glucose/galactose malabsorption since this product contains lactose.
- Are pregnant, trying to get pregnant or think you might be pregnant.
- You are breastfeeding or planning to breastfeed. Clarithromycin can get into your breast milk and harm your baby.
- Have a condition called myasthenia gravis which is a chronic disease that causes muscle weakness. Sandoz Clarithromycin XL may make your myasthenia gravis worse.
- Are taking clarithromycin and oral drugs for diabetes (such as gliclazide, glyburide) and / or with insulin as this can result in serious low blood sugar levels (hypoglycemia). Discuss with your doctor or pharmacist how you should monitor your blood sugar levels.
- Are taking warfarin, as there is a risk of serious bleeding with clarithromycin.
- Are taking triazolam, alprazolam or other benzodiazepines (midazolam). These should be used cautiously with clarithromycin due to the serious risk of effects on your brain and spinal cord.

Other warnings you should know about:

Use of antibiotics like clarithromycin have resulted in heart problems such as irregular heartbeat, torsades de pointes and QT prolongation sometimes leading to death. Talk to your doctor if you are elderly or have risk factors such as:

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

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 doctor.

Driving and using machines:
If you feel dizzy, confused or disorientated while taking Sandoz Clarithromycin XL, 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 Sandoz Clarithromycin XL:

- 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 (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).
- 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 Sandoz ClarithromycinXL:
- Take Sandoz Clarithromycin XL with food.
- Swallow Sandoz Clarithromycin XL whole, with a glass of water
- Do not break, chew, or crush the tablets.

Usual dose:
The usual adult dose is 2 x 500 mg tablets (1000 mg) every 24 hours for 5, 7 or 14 days.

Overdose:
Symptoms of Sandoz Clarithromycin XL overdose are abdominal pain, vomiting, nausea and diarrhea.

If you think you have taken too much Sandoz Clarithromycin XL, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
- If you miss a dose, take it as soon as you remember
- If it is almost time for your next dose, do not take the missed dose.
- Take your next dose when you would normally take it.
- Never take a double dose to make up for a missed dose.

What are possible side effects from using Sandoz Clarithromycin XL?

These are not all the possible side effects you may feel when taking Sandoz Clarithromycin XL. If you experience any side effects not listed here, contact 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.

If you see tablet residue in your stool, contact your doctor as your doctor may recommend a different clarithromycin formulation, especially if you have certain bowel conditions.

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.			✓
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, talk to 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 Sandoz Clarithromycin XL out of reach and sight of children.

Sandoz Clarithromycin XL should be stored between 15 and 30ºC in well closed containers, protected from light.

If you want more information about Sandoz Clarithromycin XL:

- 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.html); The sponsor's website (www.sandoz.ca) or by contacting Sandoz Canada Inc., at: 1-800-361-3062

  or by written request at:
  110 Rue de Lauzon
  Boucherville, (QC), Canada
  J4B 1E6

  or by e-mail at :
  medinfo@sandoz.com

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