PRODUCT MONOGRAPH

Pr GEN-CLARITHROMYCIN
(clarithromycin tablets, USP, film-coated)
250 mg and 500 mg

Antibiotic

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[Pr] GEN-CLARITHROMYCIN

(clarithromycin tablets, USP, film-coated)
250 mg and 500 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	film-coated tablets / 250 mg & 500 mg	colloidal silicon dioxide, croscarmellose sodium, D&C Yellow No. 10 aluminum lake, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, propylene glycol, stearic acid, titanium dioxide and vanillin.

INDICATIONS AND CLINICAL USE

GEN-CLARITHROMYCIN (clarithromycin tablets, USP, film-coated) 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

Pharyngitis/tonsillitis, caused by Streptococcus pyogenes (Group A beta-hemolytic streptococci).

Acute maxillary sinusitis caused by *Streptococcus pneumoniae (S. pneumoniae), Haemophilus influenzae (H. influenzae),* and *Moraxella (Branhamella) catarrhalis [M. (Branhamella) catarrhalis]*.

Lower Respiratory Tract

Acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae, H. influenzae* (including beta-lactamase producing strains), *M. (Branhamella) catarrhalis* (including betalactamase producing strains).

Pneumonia caused by *S. pneumoniae* and *Mycoplasma pneumoniae (M. pneumoniae).*

Uncomplicated Skin and Skin Structure Infections

Uncomplicated Skin and Skin Structure Infections caused by *Streptococcus pyogenes (S. pyogenes), Staphylococcus aureus (S. aureus).*

Mycobacterial Infections

GEN-CLARITHROMYCIN (clarithromycin tablets, USP, film-coated) is indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection (see **CLINICAL TRIALS**), and for the treatment of disseminated mycobacterial infections due to *Mycobacterium avium (M. avium)* and *Mycobacterium intracellulare (M. intracellulare).*

Geriatrics (> 65 years of age): Dosage adjustment should be considered in elderly patients with severe renal impairment. For a brief discussion please see **WARNINGS AND PRECAUTIONS** - **Geriatrics**

CONTRAINDICATIONS

GEN-CLARITHROMYCIN (clarithromycin tablets, USP, film-coated) is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, other macrolide antibacterial agents or to any ingredient in the formulation or component of the container. (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**).

Clarithromycin is contraindicated as concurrent therapy with astemizole, terfenadine, cisapride, pimozide, ergotamine or dihydroergotamine. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, astemizole, 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**).

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**.

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.

There have been postmarketing reports of colchicine toxicity with concurrent use of clarithromycin and colchicine. In patients with impaired renal function and/or who are elderly, colchicine and clarithromycin should not be used concurrently due to the risk of colchicine toxicity. Deaths have been reported in some such patients (see **Drug Interactions:** Colchicine and **ADVERSE REACTIONS**).

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

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.

Gastrointestinal

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents, including clarithromycin.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *C. difficile* is a primary cause of "antibioticassociated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management

with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug effective against *C. difficile*.

Hepatic/Biliary/Pancreatic

Clarithromycin is principally excreted by the liver and kidney (see **DOSAGE AND ADMINISTRATION**). In patients with both hepatic and renal impairments or in the presence of severe renal impairment, decreased dosage of clarithromycin or prolonged dosing intervals might be appropriate.

Renal

Clarithromycin is principally excreted by the liver and kidney (see **DOSAGE AND ADMINISTRATION**). In patients with both hepatic and renal impairments or in the presence of severe renal impairment, decreased dosage of clarithromycin or prolonged dosing intervals might be appropriate.

Sensitivity/Resistance

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

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**). Four teratogenicity studies in rats (three with oral doses and one with
intravenous doses up to 160 mg/kg/day administered during the period of major organogenesis) and two in rabbits (at oral doses up to 125 mg/kg/day 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 - 12 years of age)

Use of clarithromycin 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 agerelated 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 tablets were of a mild and transient nature. Fewer than 3% of adult patients without mycobacterial infections discontinued therapy because of drug-related side-effects. The most common drug-related adverse reactions in adults taking clarithromycin tablets were nausea, diarrhea, abdominal pain , dyspepsia, headache, taste perversion and vomiting.

Clinical Trial Adverse Drug Reactions
General Statement

> *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.*

GEN-CLARITHROMYCIN (clarithromycin tablets, USP, film-coated)

Patients with Respiratory Tract or Skin Infections

Adverse Reactions

Table 1	
Patients with Respiratory Tract or Skin Infections – CLARITHROMYCIN TABLETS	
System Organ Class	**Adverse Reaction/Adverse Event***
General disorders and administration site conditions	Asthenia Pain Chest pain
Infections and infestations	Infection Colitis pseudomembranous Candidiasis Rhinitis Pharyngitis Vaginal candidiasis Vaginal infection
Musculoskeletal and connective tissue disorders	Back pain
Investigations	Electrocardiogram QT prolonged Increased liver enzymes
Cardiac disorders	Ventricular tachycardia Torsades de pointes
Gastrointestinal disorders	Constipation Flatulence Dry mouth Glossitis Stomatitis Gastrointestinal disorder Tongue discolouration Tooth discolouration Pancreatitis
Metabolism and nutrition disorders	Anorexia Hypoglycemia
Hepatobiliary disorders	Hepatomegaly Hepatic function abnormal Hepatitis Hepatitis cholestatic Jaundice Hepatic failure
Nervous system disorders	Dizziness Somnolence Convulsion Parosmia Dysgeusia Ageusia
Ear and labyrinth disorders	Vertigo Tinnitus Ear disorder Deafness**
Psychiatric disorders	Nervousness Anxiety Insomnia Nightmare Depression Confusional state Disorientation Depersonalisation Hallucination Psychotic disorder

Table 1	
Patients with Respiratory Tract or Skin Infections – CLARITHROMYCIN TABLETS	
System Organ Class	**Adverse Reaction/Adverse Event***
Respiratory, thoracic and mediastinal disorders	Cough Dyspnea Asthma
Skin and subcutaneous tissue disorders	Pruritis Rash Hyperhidrosis Urticaria Stevens-Johnson syndrome Toxic epidermal necrosis
Immune system disorders	Anaphylactic reaction
Eye disorders	Visual disturbance Conjunctivitis
Renal and urinary disorders	Hematuria Nephritis interstitial
Reproductive system and breast disorders	Dysmenorrhea
Blood and lymphatic system disorders	Eosinophilia Anemia Leukopenia Thrombocythemia Thrombocytopenia
* Adverse reactions from clinical trials or post-marketing surveillance and adverse events reported during post-marketing surveillance. Adverse events reported during post-marketing surveillance may include patients treated for various infections and are not be limited to patients with respiratory tract or skin infections. ** There have been reports of hearing loss with clarithromycin which is usually reversible upon withdrawal of therapy.	

In studies of adults with pneumonia comparing clarithromycin to erythromycin base or erythromycin stearate, there were significantly fewer adverse events involving the digestive system in patients treated with clarithromycin.

Abnormal Laboratory Values

Changes in laboratory values with possible clinical significance reported during clinical studies or during post-marketing surveillance are displayed in **Table 2**.

Table 2 **Abnormal Hematologic and Clinical Chemistry Findings in Patients with Respiratory Tract or Skin Infections Treated with CLARITHROMYCIN TABLETS**		
System Organ Class	**Laboratory Values**	**Frequency**
Investigations	Alanine aminotransferase increased Aspartate aminotransferase increased Gamma-glutamyltransferase increased Blood alkaline phosphatase increased Blood lactate dehydrogenase increased Blood bilirubin increased Blood creatinine increased White blood cell count decreased	Uncommon (Less than 1%)
	Prothrombin time prolonged	1%
	Blood urea increased	4%

Patients with Mycobacterial Infections

In patients with acquired immune deficiency syndrome (AIDS) and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for prevention or treatment of mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of HIV disease or intercurrent illness. Other adverse reactions have been observed in different patient populations and during post-marketing surveillance. Please also refer to **ADVERSE REACTIONS** - Patients with Respiratory Tract or Skin Infections.

Prophylaxis

Adverse Reactions

Discontinuation due to adverse events was required in 18% of AIDS patients receiving clarithromycin 500 mg b.i.d., compared to 17% of patients receiving placebo in a randomized, double-blind study. Primary reasons for discontinuation in the clarithromycin-treated patients include headache, nausea, vomiting, depression and taste perversion. The most frequently reported adverse events with an incidence of 2% or greater, excluding those due to the patient's concurrent condition, are listed in **Table 3**. Among these events, taste perversion was the only event that had significantly higher incidence in the clarithromycin-treated compared to the placebo-treated group.

Table 3
Percentage of Adverse Events* in Immunocompromised Adult Patients Receiving Prophylaxis Against *M. avium* Complex

System Organ Class‡	Adverse Reaction	Clarithromycin (n=339) %	Placebo (n=339) %
Gastrointestinal disorders	Abdominal pain	5.0%	3.5%
	Nausea	11.2%	7.1%
	Diarrhea	7.7%	4.1%
	Vomiting	5.9%	3.2%
	Dyspepsia	3.8%	2.7%
	Flatulence	2.4%	0.9%
Nervous system disorders	Dysgeusia	8.0%	0.3%
	Headache	2.7%	0.9%
Skin and subcutaneous tissue disorders	Rash	3.2%	3.5%

* Includes those events possibly or probably related to study drug and excludes concurrent conditions.
‡ ≥ 2% Adverse Event Incidence Rates for either treatment group.

Abnormal Laboratory Values

In immunocompromised patients receiving prophylaxis against *M. avium*, those laboratory values outside the extreme high or low limit for the specified test were analyzed (see **Table 4**).

Table 4
Percentage of Patients* Exceeding Extreme Laboratory Value in Patients Receiving Prophylaxis Against *M. avium* Complex

System Organ Class	Laboratory Values	Clarithromycin 500 mg b.i.d.		Placebo	
Investigations	Hemoglobin decreased <8 g/dL	4/118	3%	5/103	5%
	Platelet count decreased $<50 \times 10^9$/L	11/249	4%	12/250	5%
	White blood cell count decreased $<1 \times 10^9$/L	2/103	4%	0/95	0%
	Aspartate aminotransferase increased >5 × ULN**	7/196	4%	5/208	2%
	Alanine aminotransferase increased >5 × ULN**	6/217	3%	4/232	2%
	Blood alkaline phosphatase increased >5 × ULN**	5/220	2%	5/218	2%

* Includes only patients with baseline values within the normal range or borderline high (hematology variables) and within the normal range or borderline low (chemistry variables).

** ULN - Upper Limit of Normal.

Treatment of Patients with Mycobacterial Infections

Adverse Reactions

Excluding those patients who discontinued therapy due to complications of their underlying non-mycobacterial diseases (including death), approximately 14% of the patients discontinued therapy due to drug-related adverse events.

In adult patients, the most frequently reported adverse events with an incidence of 3% or greater, excluding those due to the patient's concurrent condition, are listed in **Table 5** by the total daily dose the patient was receiving at the time of the event. A total of 867 patients were treated with clarithromycin for mycobacterial infections. Of these, 43% reported one or more adverse events. Most of these events were described as mild to moderate in severity, although 14% were described as severe.

Incidence of adverse events was higher in patients taking 4000 mg total daily doses compared to lower doses (see **Table 5**).

Table 5 Percentage of Adverse Events* in Immunocompromised Adult Patients Treated with Clarithromycin for Mycobacterial Infections				
Presented by Total Daily Dose at Time of the Event				
System Organ Class	**Adverse Reaction**	**1000 mg (n=463)**	**2000 mg (n=516)**	**4000 mg (n=87)**
Gastrointestinal disorders	Nausea	11%	16%	40%
	Vomiting	7%	9%	24%
	Abdominal Pain	5%	7%	20%
	Diarrhea	4%	6%	17%
	Flatulence	1%	2%	7%
	Constipation	1%	<1%	5%
	Dry Mouth	<1%	0%	5%
Nervous system disorders	Dysgeusia	6%	7%	29%
	Headache	2%	2%	7%
Skin and subcutaneous tissue disorders	Rash	4%	3%	2%
Investigations	Aspartate aminotransferase increased	2%	2%	11%
	Alanine aminotransferase increased	1%	1%	9%
Respiratory, thoracic and mediastinal disorders	Dyspnea	<1%	<1%	7%
Psychiatric disorders	Insomnia	<1%	<1%	6%
Ear and labyrinth disorders	Hearing impaired**	3%	2%	5%
* Related adverse events considered to be definitely, probably, possibly or remotely related to study events. ** Sum of patients with deafness, ear disorder, partial transitory deafness, and/or tinnitus. n = Number of adverse events.				

Abnormal Laboratory Values

In immunocompromised patients treated with clarithromycin for mycobacterial infections, evaluations of laboratory values were made by analysing those values outside the seriously abnormal level (i.e., the extreme high or low limit) for the specified test (see **Table 6**).

Table 6
Percentage of Immunocompromised Adult Patients Treated with Clarithromycin for Mycobacterial Infections who had On-Treatment Laboratory Values that Were Outside the Seriously Abnormal Level

Presented by Total Daily Dose					
System Organ Class	**Laboratory Values**	**Seriously Abnormal Level**	**1000 mg**	**2000 mg**	**4000 mg**
Investigations	Aspartate aminotransferase increased	>5 × ULN	3%	2%	4%
	Alanine aminotransferase increased	>5 × ULN	2%	2%	7%
	Platelet count decreased	$<50 \times 10^9$/L	2%	2%	4%
	White blood cell count decreased	$<1 \times 10^9$/L	0%	2%	0%
	Blood urea increased	>50 mg/dL	<1%	<1%	4%

ULN = Upper Limit of Normal.

Post-Market Adverse Drug Reactions

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

Table 7 **Post-Market Adverse Drug Reactions**	
System Organ Class	**Adverse Event**
Blood and lymphatic system disorders	Leukopenia
	Thrombocytopenia
Investigations	Electrocardiogram QT prolonged
Cardiac disorders	Ventricular tachycardia
	Torsades de pointes
Gastrointestinal disorders	Dyspepsia
	Vomiting
	Glossitis
	Stomatitis
Infections and infestations	Candidiasis
Gastrointestinal disorders	Tongue discolouration
	Tooth discolouration
	Pancreatitis
Hepatobiliary disorders	Hepatic function abnormal
	Hepatitis
	Hepatitis cholestatis
	Hepatic failure
	Jaundice
Investigations	Increased liver enzymes
Metabolism and nutrition disorders	Hypoglycemia
Nervous system disorders	Dizziness
	Vertigo
	Alteration of sense of smell
	Convulsions
Psychiatric disorders	Anxiety
	Insomnia
	Bad dreams
	Confusion
	Disorientation
	Hallucination
	Psychosis
	Depersonalization
Skin and subcutaneous tissue disorders	Urticaria
	Mild skin eruptions
	Stevens Johnson syndrome
	Toxic epidermal necrosis
Immune system disorders	Anaphylaxis
Ear and labyrinth disorders	Tinnitus
	Hearing loss
Renal and urinary disorders	Interstitial nephritis

DRUG INTERACTIONS

Serious Drug Interactions

- Concomitant administration of clarithromycin with astemizole, cisapride, pimozide, terfenadine, ergotamine, or dihydroergotamine is contraindicated (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).
- Clarithromycin is an inhibitor of CYP3A4. The concomitant administration of clarithromycin and drugs metabolized by this enzyme (or enzyme system) 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 the cytochrome P450 3A4 enzyme located in the liver and in the intestine. Some drugs inhibit and others induce this enzyme. Co-administration of such drugs may impact upon each other's metabolism. In some cases serum concentration may be increased and in others decreased. Care must therefore be exercised when co-administering such drugs.

Clarithromycin is reported to be an inhibitor of the enzyme P450 3A4. This may lead to increased or prolonged serum levels of those drugs also metabolized by the enzyme when co-administered with clarithromycin. For such drugs the monitoring of their serum concentrations may be necessary.

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 9. Like clarithromycin and omeprazole, most of the following drugs are metabolized by the P450 3A4 enzyme system.

Additional mechanisms, such as effects upon absorption, may also be responsible for interaction between drugs, including digoxin and clarithromycin.

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

Table 8 Established or Potential Drug-Drug Interactions			
Clarithromycin	**Ref**	**Effect**	**Clinical Comments**
Astemizole / Terfenadine	CT	terfenadine-acid metabolite concentrations increase ↑ QT interval	Macrolides have been reported to alter the metabolism of terfenadine resulting in increased serum levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsade de pointes (see **CONTRAINDICATIONS**). In a study involving 14 healthy volunteers, the concomitant administration of clarithromycin tablets and terfenadine resulted in a two to three-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.
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 may 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 (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicines toxicity (see **WARNINGS AND PRECAUTIONS: General** and **ADVERSE REACTIONS**).

Table 8 Established or Potential Drug-Drug Interactions			
Cyclosporine	C	↑ levels of cyclosporine	There have been reports of elevated cyclosporine serum concentrations when clarithromycin and cyclosporine are used concurrently. Cyclosporine levels should be monitored and the dosage should be adjusted as necessary. Patients should also be monitored for increased cyclosporine toxicity.
Didanosine	CT	No change in didanosine pharmacokinetics in HIV-infected patients (n=12)	Simultaneous administration of clarithromycin tablets and didanosine to 12 HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.
Digoxin	C	↑ levels of digoxin	Elevated digoxin serum concentrations have been reported in patients receiving clarithromycin tablets and digoxin concomitantly. In post-marketing surveillance some patients have shown clinical signs consistent with digoxin toxicity, including arrhythmias. Serum digoxin levels should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.
Disopyramide / Quinidine	C	↑ levels of disopyramide, resulting ventr. 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 has rarely been reported. There have been postmarketed reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Serum levels of these medications should be monitored during clarithromycin therapy.
Ergotamine / Dihydroergotamine	C	Potential ischemic reactions Potential ergot toxicity	There are reports that ischemic reactions may occur when clarithromycin is given concurrently with ergotamine-containing drugs. Concurrent use of clarithromycin and ergot alkaloids has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia. (see **CONTRAINDICATIONS**)

Table 8 Established or Potential Drug-Drug Interactions			
Fluconazole	CT	↑ clarithromycin C_{min} & AUC	Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state clarithromycin C_{min} and AUC of 33% and 18%, respectively. Steady-state concentrations of 14-OH clarithromycin were not significantly affected by concomitant administration of fluconazole.
Lansoprazole / Omeprazole	CT	Mild change of lansoprazole and 14-OH clarithromycin concentrations	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.
		↑ omeprazole C_{max}& AUC_{0-24}	Clarithromycin 500 mg t.i.d. was given in combination with omeprazole 40 mg q.d. to healthy subjects. The steady-state plasma concentrations of omeprazole were increased (i.e., C_{max}, AUC_{0-24}, and $t_{1/2}$ increased by 30%, 89%, and 34%, respectively), by concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when co-administered with clarithromycin.
		↑ levels of clarithromycin	To a lesser extent, omeprazole administration increases the serum concentrations of clarithromycin, Omeprazole administration aslso increases tissue and mucus concentrations of clarithromycin.
Lovastatin / Simvastatin	C	Rhabdomyolysis (rarely reported)	Rhabdomyolysis coincident with the co-administration of clarithromycin and the HMG-CoA reductase inhibitors, lovastatin and simvastatin, has rarely been reported.
Atorvastatin	C		Concurrent use of atorvastatin and clarithromycin may result in increased atorvastatin exposure and an increased risk of rhabdomyolysis.
Midazolam / Triazolam	C	↓ clearance of midazolam & triazolan	Clarithromycin has been reported to decrease the clearance of midazolam and triazolam and thus may increase the pharmacologic effect of these drugs.

Table 8 Established or Potential Drug-Drug Interactions			
Rifabutin / Rifampin	C	↓ levels of clarithromycin ↑ levels of rifabutin	Co-administration of rifabutin or rifampin and clarithromycin has resulted in decreased clarithromycin concentrations. Clarithromycin has been reported to increase serum and tissue concentration of rifabutin and thus may increase the risk of toxicity.
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 q8h and clarithromycin 500 mg q12h 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 CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1gm/day should not be coadministered with ritonavir. 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.
Tacrolimus	P	Potential ↑ in tacrolimus concentrations	Concomitant administration of tacrolimus and clarithromycin may result in increased plasma levels of tacrolimus and increased risk of toxicity.

Table 8 Established or Potential Drug-Drug Interactions			
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.
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.
Zidovudine	C	Potential ↓ in zidovudine concentrations	Simultaneous oral administration of clarithromycin 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, therefore this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine.
Others / Drugs metabolized by cytochrome P_{450} system	C/P	Potential change in serum concentration	Interactions with erythromycin and/or clarithromycin have been reported with a number of other drugs metabolized by the cytochrome P_{450} system, such as alfentanil, alprazolam, bromocriptine, cilostazol, hexobarbital, methylprednisolone, phenytoin, sildenafil, valproate or vinblastine. Serum concentrations of drugs metabolized by the cytochrome P_{450} system should be monitored closely in patients concurrently receiving erythromycin or clarithromycin.
Legend: C = Case Study; CT = Clinical Trial; P = Potential Interactions with other drugs have not been established.			

Drug-Food Interactions

GEN-CLARITHROMYCIN Tablets, USP, film-coated may be given with or without meals.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

GEN-CLARITHROMYCIN Tablets, USP, film-coated may be given with or without meals.

In patients with both hepatic and renal impairments or in the presence of severe renal impairment, decreased dosage of clarithromycin or prolonged dosing intervals might be appropriate (see **Recommended Dose and Dosage Adjustment**).

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

Recommended Dose and Dosage Adjustment

GEN-CLARITHROMYCIN (clarithromycin tablets, USP, film-coated)

Adults with Respiratory Tract or Skin Infections

The adult dosage of GEN-CLARITHROMYCIN is 250 mg to 500 mg every 12 hours (see **Table 9)** for 7 to 14 days. For infections caused by less susceptible organisms, the upper dosage should be used.

Table 9 Adult Dosage Guidelines		
Infection	**Dosage (b.i.d.)**	**Duration**
Upper Respiratory Tract Pharyngitis/tonsillitis Acute maxillary sinusitis	**250-500 mg** 250 mg 500 mg	10 days 7-14 days
Lower Respiratory Tract Acute exacerbation of chronic bronchitis and pneumonia	**250-500 mg** 250-500 mg	7-14 days
Uncomplicated Skin and Skin Structure Infections	**250 mg**	7-14 days

In the treatment of Group A streptococcus infections, therapy should be continued for 10 days. The usual drug of choice in the treatment of streptococcal infections and the prophylaxis of rheumatic fever is penicillin administered by either the *i.m* or the oral route.

Clarithromycin is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of clarithromycin in the subsequent prevention of rheumatic fever are not presently available.

Renal Impairment

In patients with renal impairment and a creatinine clearance less than 30 mL/min., the dosage of GEN-CLARITHROMYCIN should be reduced by one-half, i.e., 250 mg once daily, or 250 mg twice daily in more severe infections. Dosage should not be continued beyond 14 days in these patients. The safety and efficacy of 500 mg clarithromycin in patients with severe renal impairment has not been established.

Hepatic Impairment

In patients with both hepatic and renal impairments or in the presence of severe renal impairment, decreased dosage of clarithromycin or prolonged dosing intervals may be appropriate. Clarithromycin may be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function.

Adults with Mycobacterial Infections

Prophylaxis

The recommended dose of GEN-CLARITHROMYCIN for the prevention of disseminated *M. avium* disease is 500 mg b.i.d.

Treatment

Clarithromycin is recommended as the primary agent for the treatment of disseminated infection due to MAC. Clarithromycin should be used in combination with other antimycobacterial drugs

which have shown *in vitro* activity against MAC, including ethambutol and rifampin. Although no controlled clinical trial information is available for combination therapy with clarithromycin, the U.S. Public Health Service Task Force has provided recommendations for the treatment of MAC.

The recommended dose for mycobacterial infections in adults is 500 mg b.i.d.

Treatment of disseminated MAC infections in AIDS patients should continue for life if clinical and mycobacterial improvement are observed.

Missed Dose

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

Administration

GEN-CLARITHROMYCIN may be taken with or without food.

OVERDOSAGE

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 Tablets, USP, film-coated

A summary of clarithromycin pharmacokinetic parameters following the administration of

clarithromycin film-coated tablets is provided in **Table 10**. For details see **DETAILED PHARMACOLOGY** in PART II of the Product Monograph.

Table 10
Clarithromycin Pharmacokinetic Parameters
following the Administration of Clarithromycin Film-coated Tablets

Single dose*	**C_{max}** (mg/L)	**t_{max}** (hr)	**$t_{½}$** (hr)	**AUC_{0-t}** (mg·hr/L)
250 mg Mean	1	1.5	2.7	5.47
500 mg Mean	1.77	2.2	---	11.66
Multiple Doses**				
250 mg b.i.d. Mean	1	---	3 to 4	6.34
500 mg b.i.d. Mean	3.38	2.1	5 to 7	44.19

* Single doses (from **Tables 56** & **57**)
** Multiple doses (from **Tables 48** & **57**)

Absorption

Clarithromycin Film-Coated Tablets

The absolute bioavailability of 250 mg and 500 mg clarithromycin tablets is approximately 50%. Food slightly delays the onset of clarithromycin absorption but does not affect the extent of bioavailability. Therefore, GEN-CLARITHROMYCIN may be given without regard to meals.

In fasting healthy human subjects, peak serum concentrations are attained within 2 hours after oral dosing. Steady-state peak serum clarithromycin concentrations, which are attained within 2 to 3 days, are approximately 1 mg/L with a 250 mg dose twice daily and 2 to 3 mg/L with a 500 mg dose twice daily. The elimination half-life of clarithromycin is about 3 to 4 hours with 250 mg twice daily dosing but increases to about 5 to 7 hours with 500 mg administered twice daily.

Clarithromycin displays non-linear pharmacokinetics at clinically relevant doses, producing greater than proportional increases in AUC with increasing dose. The degree of non-linearity is reduced on chronic clarithromycin administration (i.e., at steady state). The non-linearity of the pharmacokinetics of the principle metabolite, 14-OH clarithromycin, is slight at the recommended doses of 250 mg and 500 mg administered twice daily. With 250 mg twice daily, 14-OH clarithromycin attains a peak steady state concentration of about 0.6 mg/L and has an elimination half-life of 5 to 6 hours. With a 500 mg twice daily dose, the peak steady-state of 14-OH concentrations of clarithromycin are slightly higher (up to 1 mg/L) and its elimination half-life is about 7 hours. With either dose, the steady-state concentration of this metabolite is generally attained within 2 to 3 days.

Adult Patients with HIV. Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of 500 mg doses of clarithromycin twice a day to adult patients with HIV infection were similar to those observed in healthy volunteers. However, at the higher clarithromycin doses which may be required to treat mycobacterial infections, clarithromycin concentrations can be much higher than those observed at 500 mg clarithromycin doses. In adult HIV-infected patients taking 2000 mg/day in two divided doses, steady-state clarithromycin C_{max} values ranged from 5 to10 mg/L. C_{max} values as high as 27 mg/L have been observed in HIV-infected adult patients taking 4000 mg/day in two divided doses of clarithromycin tablets.

Elimination half-lives appeared to be lengthened at these higher doses as well. The higher clarithromycin concentrations and longer elimination half-lives observed at these doses are consistent with the known non-linearity in clarithromycin pharmacokinetics.

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 11.**

Table 11
Representative Clarithromycin Tissue and Serum Concentrations Following the Administration of 250 mg b.i.d of Clarithromycin Film-Coated Tablets

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

* *in vitro* data.

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 5-10% 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 **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency

The elimination of clarithromycin was impaired in patients subjects with impaired renal function (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). The daily dose of clarithromycin should be limited to 500 mg in patients with severe renal impairment (CRCL < 30 mL/min).

STORAGE AND STABILITY

GEN-CLARITHROMYCIN (clarithromycin tablets, USP, film-coated)
Store between 15 and 30°C in a tightly closed container. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

GEN-CLARITHROMYCIN (clarithromycin tablets, USP, film-coated)

Medicinal Ingredient:
250 mg: Each yellow, oval, biconvex, film-coated tablet with “C250” on one side and “G” on the other side contains 250 mg of clarithromycin for oral administration.
500 mg: Each pale yellow, oval, biconvex, film-coated tablet with “C500” on one side and “G” on the other side contains 500 mg of clarithromycin for oral administration

Non-Medicinal Ingredients: Each GEN-CLARITHROMYCIN also contains the following non-medicinal ingredients:

250 mg and 500 mg: Colloidal silicon dioxide, croscarmellose sodium, D&C yellow No. 10 aluminum lake, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, propylene glycol, stearic acid, titanium dioxide and vanillin. GEN-CLARITHROMYCIN does not contain tartrazine.

PACKAGING

GEN-CLARITHROMYCIN (clarithromycin tablets, USP, film-coated) are supplied in HDPE bottles of 100 and 500 tablets as yellow, oval, biconvex, film-coated tablets "C250" on one side and "G" on the other side containing 250 mg of clarithromycin, and HDPE bottles of 100 tablets as pale yellow, oval, biconvex, film-coated tablet with "C500" on one side and "G" on the other side containing 500 mg of clarithromycin.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

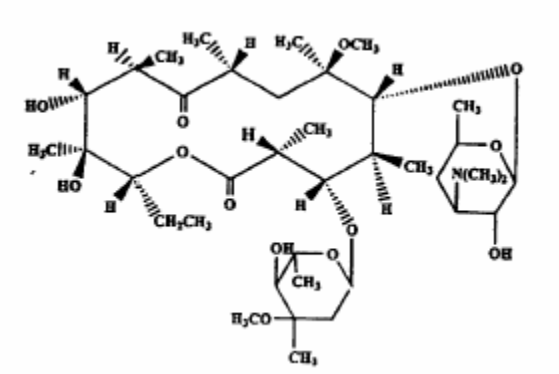
Proper name: Clarithromycin USP

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

Structural formula:



Physicochemical properties: Clarithromycin is a white to off-white crystalline powder. Soluble in acetone; slightly soluble in dehydrated alcohol, in methanol, and in acetonitrile; practically insoluble in water. Slightly soluble in phosphate buffer at pH values of 2 to5.

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 co-efficient varies from 5.63 to 46.0 for pH water increases from 2 to 8. The melting point of clarithromycin is approximately 225°C.

CLINICAL TRIALS

Single-dose, randomized, 2-way crossover bioequivalence studies under fasted and fed conditions were performed using 21 fasting and 35 fed normal healthy adult male subjects to compare the bioavailability of Gen-Clarithromycin Tablets, 500 mg (Genpharm Inc., Canada) and that of Biaxin® BID Tablets, 500 mg (Abbott Laboratories, Ltd., Canada) as a 1 X 500 mg tablet. The results of the two studies are summarized in the following tables:

SUMMARY TABLE OF
THE COMPARATIVE BIOAVAILABILITY DATA
SINGLE-DOSE, RANDOMIZED, 2-WAY, FASTING STUDY
Clarithromycin (1 X 500 mg)
From Measured Data

Clarithromycin 1 X 500 mg Fasted conditions, from measured data **Geometric Mean Arithmetic Mean (CV%)**				
Parameter	Test*	Reference‡	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-T} (ng.h/mL)	12245 12928 (35)	12116 12886 (36)	101	92% – 110%
AUC_{0-inf} (ng.h/mL)	12476 13168 (35)	12400 13171 (36)	100	92% – 110%
C_{max} (ng/mL)	1869 1972 (34)	1762 1934 (41)	106	92% - 122%
T_{max} (h)§	1.74 (35)	2.13 (50)	-	-
$T_{½}$ (h) §	4.13 (19)	4.13 (20)	-	-

***** Gen-Clarithromycin Tablets, 500 mg (Genpharm Inc., Canada).
‡ Biaxin® BID Tablets, 500 mg (Abbott Laboratories, Ltd., Canada), purchased in Canada.
§ Expressed as arithmetic mean (CV%) only.

SUMMARY TABLE OF
THE COMPARATIVE BIOAVAILABILITY DATA
SINGLE-DOSE, RANDOMIZED, 2-WAY, FED STUDY
Clarithromycin (1 X 500 mg)
From Measured Data

Clarithromycin 1 X 500 mg Fed conditions, from measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference‡	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-T} (ng.h/mL)	14915.97 15973.32 (36.5)	14733.75 15848.92 (41.7)	101	94% – 109%
AUC_{0-inf} (ng.h/mL)	15346.17 16462.31 (37.0)	15168.71 16310.42 (41.2)	101	93% – 109%
C_{max} (ng/mL)	2347.55 2537.66 (38.6)	2234.19 2421.26 (42.6)	105	94% - 117%
T_{max} (h)§	2.41 (46.4)	2.56 (49.7)	-	-
$T_{½}$ (h) §	4.41 (20.5)	4.41 (19.4)	-	-

***** Gen-Clarithromycin Tablets, 500 mg (Genpharm Inc., Canada).
‡ Biaxin® BID Tablets, 500 mg (Abbott Laboratories, Ltd., Canada), purchased in Canada.
§ Expressed as arithmetic mean (CV%) only.

Mycobacterial Infections

Prophylaxis

Table 12 Summary of Demographics and Trial Design Prophylaxis Against *M. avium*Complex				
Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects Immunocompromised patients with CD_4 counts <100 cells/µL**	**Mean age (Range)**
561	Double-blind	clarithromycin 500 mg b.i.d (≈10.6 mo) Placebo b.i.d (8.2 mo)	341 341	Adult

More patients in the placebo arm than the clarithromycin arm discontinued prematurely from the study (75.6% and 67.4%, respectively). However, if premature discontinuations due to *Mycobacterium avium* complex (MAC) or death are excluded, approximately equal percentages of patients on each arm (54.8% on clarithromycin and 52.5% on placebo) discontinued study drug early for other reasons.

Table 13 Summary of Efficacy Results in Immunocompromised Adult Patients Receiving Prophylaxis Against *M. avium* Complex					
	Clarithromycin	**Placebo**	**Hazard Ratio (95% CI)**	**p-value**	**Risk reduction**
MAC bacteremia					
# patients developed MAC	19/333 (5.7%)	53/334 (15.9%)	0.307 (0.177, 0.533)	< 0.001*	- 69.3%
Survival					
# patients died	106/341 (31.1%)	136/341 (39.9%)	0.710 (0.533, 0.934)	0.014*	- 28.2%
Emergence of MAC Signs/Symptoms					
	# meeting criterion/total	# meeting criterion/total			
Wt. loss >10%	5/333 (2%)	23/322 (7%)	0.179 (0.067, 0.481)	0.001*	- 82.1%
Moderate/severe pyrexia	2/332 (<1%)	10/329 (3%)	0.191 (0.041, 0.883)	0.034*	- 80.9%
Moderate/severe night sweats	1/325 (<1%)	7/327 (2%)	0.130 (0.016, 1.081)	0.059	- 87.0%
Mod./severe night sweats or pyrexia	2/325 (<1%)	13/326 (4%)	0.140 (0.031, 0.632)	0.011*	- 86.0%
Moderate/severe anemia	0/319 (0%)	12/321 (4%)	0		
Grade 3 or 4 LFT	3/325 (<1%)	2/318 (<1%)	0.739 (0.118, 4.649)	0.747	

Table 13 **Summary of Efficacy Results in Immunocompromised Adult Patients Receiving Prophylaxis Against *M. avium* Complex**					
Quality of Life Subscores (time to first decrease of $ 10 points)					
	# meeting criterion/total	# meeting criterion/total			
Overall health	180/317 (57%)	184/318 (58%)	0.809 (0.645, 1.015)	0.068	
Physical function	210/299 (70%)	236/306 (77%)	0.781 (0.637, 0.956)	0.017*	- 21.9%
Role function	111/189 (59%)	131/211 (62%)	0.922 (0.690, 1.233)	0.585	
Social function	187/327 (57%)	197/331 (60%)	0.823 (0.662, 1.024)	0.08	
Cognitive function	174/336 (52%)	170/339 (50%)	0.990 (0.790, 1.240)	0.929	
Pain	201/331 (61%)	217/336 (65%)	0.902 (0.731, 1.113)	0.355	
Mental Health	179/336 (53%)	184/338 (54%)	0.842 (0.672, 1.055)	0.134	
Energy/fatigue	208/328 (63%)	217/335 (65%)	0.784 (0.636, 0.966)	0.022*	- 21.6%
Health distress	170/335 (51%)	191/335 (57%)	0.807 (0.647, 1.007)	0.057	
Quality of life	199/330 (60%)	199/333 (60%)	0.902 (0.727, 1.120)	0.352	
Hospitalization					
# patients	166/339 (49%)	189/330 (57%)	0.764 (0.610, 0.955)	0.018*	- 23.6%
hospitalized					

On an intent-to-treat basis, the one-year cumulative incidence of MAC bacteremia was 5.0% for patients randomized to clarithromycin and 19.4% for patients randomized to placebo (see **Table 14**). While only 19 of the 341 patients randomized to clarithromycin developed MAC, 11 of these cases were resistant to clarithromycin. The patients with resistant MAC bacteremia had a median baseline CD_4 count of 10 cells/mm3 (range 2 to 25 cells/mm^3). Information regarding the clinical course and response to treatment of the patients with resistant MAC bacteremia is limited. The 8 patients who received clarithromycin and developed susceptible MAC bacteremia had a median baseline CD_4 count of 25 cells/mm^3 (range 10 to 80 cells/mm^3). Comparatively, 53 of the 341 placebo patients developed MAC; none of these isolates were resistant to clarithromycin. The median baseline CD_4 count was 15 cells/mm^3 for placebo patients that developed MAC.

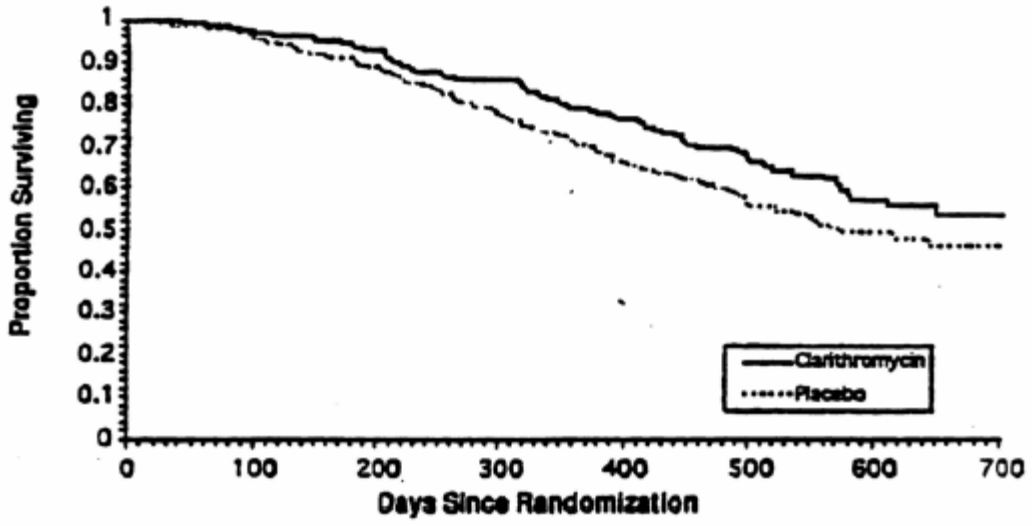


Figure 1 : Survival of All Randomized Immunocompromized Adult Patients Receiving Clarithromycin in Prophylaxis Against *M. avium* Complex or Placebo

Table 14
Cumulative Incidence of MAC Bacteremia and Mortality in Immunocompromised Adult Patients Receiving Prophylaxis Against *M. avium* Complex

	Cumulative Incidence of MAC Bacteremia*		**Cumulative Mortality**	
	Clarithromycin	Placebo	Clarithromycin	Placebo
6 month	1.0 %	9.5 %	6.4 %	9.3 %
12 month	5.0 %	19.4 %	20.8 %	29.7 %
18 month	10.1 %	26.8 %	36.8 %	46.8 %
* from Kaplan-Meier estimates.				

Since the analysis at 18 months includes patients no longer receiving prophylaxis the survival benefit of clarithromycin may be underestimated.

Treatment of Mycobacterial Infections

Three studies summarized in **Table 15** were designed to evaluate the following end points:

- Change in MAC bacteremia or blood cultures negative for *M. avium*.
- Change in clinical signs and symptoms of MAC infection including one or more of the following: fever, night sweats, weight loss, diarrhea, splenomegaly, and hepatomegaly.

Table 15
Summary of Demographics and Trial Design
Efficacy of Clarithromycin in the Treatment of Mycobacterial Infections

Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (n=number)**	**Mean age (Range)**
500	Randomized, double-blind	500 mg b.i.d 1000 mg b.i.d 2000 mg b.i.d.	CDC-defined AIDS and CD_4 counts <100 cells/µL (n=154)	Adult
577	Open -label*	500 mg b.i.d 1000 mg b.i.d	CDC-defined AIDS and CD_4 counts <100 cells/µL (n=469)	Adult
* compassionate use.				

The results of the Study 500 are described below. The Study 577 results were similar to the results of the Study 500.

MAC bacteremia. Decreases in MAC bacteremia or negative blood cultures were seen in the majority of patients in all dose groups. Mean reductions in colony forming units (CFU) are shown below. Included in the table are results from a separate study with a four drug regimen (ciprofloxacin, ethambutol, rifampicin, and clofazimine). Since patient populations and study procedures may vary between these two studies, comparisons between the clarithromycin results and the combination therapy results should be interpreted cautiously (see **Table 16**).

Table 16 Mean Reductions in Log CFU from Baseline (After 4 Weeks of Therapy)			
500 mg b.i.d.	**1000 mg b.i.d.**	**2000 mg b.i.d.**	**Four Drug Regimen**
(N=35)	(N=32)	(N=26)	(N=24)
1.5	2.3	2.3	1.4

Although the 1000 mg and 2000 mg b.i.d. doses showed significantly better control of bacteremia during the first four weeks during therapy, no significant differences were seen beyond that point. The percent of patients whose blood was sterilized as shown by one or more negative cultures at any time during acute therapy was 61% (30/49) for the 500 mg b.i.d. group and 59% (29/49) and 52% (25/28) for the 1000 and 2000 mg b.i.d. groups, respectively. The percent of patients who had 2 or more negative cultures during acute therapy that were sustained through study Day 84 was 25% (12/49) in both the 500 and 1000 mg b.i.d. groups and 8% (4/48) for the 2000 mg b.i.d. group. By Day 84, 23% (11/49), 37% (18/49), and 56% (27/48) of patients had died or discontinued from the study, and 14% (7/49), 12% (6/49), and 13% (6/48) of patients had relapsed in the 500, 1000, and 2000 mg b.i.d. dose groups, respectively. All of the isolates had a minimum inhibitory concentration (MIC) <8 mcg/mL at pretreatment. Relapse was almost always accompanied by an increase in MIC. The median time to first negative culture was 54, 41, and 29 days for the 500, 1000, and 2000 mg b.i.d. groups, respectively.

Clinically significant disseminated MAC Disease. Among patients experiencing night sweats prior to therapy, 84% showed resolution or improvement at some point during the 12 weeks of clarithromycin at 500 to 2000 mg b.i.d. doses. Similarly, 77% of patients reported resolution or improvement in fevers at some point. Response rates for clinical signs of MAC are given in **Table 17.**

Table 17 Response Rates for Clinical Signs of MAC					
Resolution of Fever			**Resolution of Night Sweats**		
b.i.d. dose (mg)	% ever afebrile	% afebrile ≥ 6 weeks	b.i.d dose (mg)	% ever resolving	% resolving ≥ 6 weeks
500	67	23	500	85	42
1000	67	12	1000	70	33
2000	62	22	2000	72	36
Weight Gain >3%			**Hemoglobin Increase >1 g**		
b.i.d. dose (mg)	% ever gaining	% gaining ≥ 6 weeks	b.i.d. dose (mg)	% ever increasing	%increasing ≥ 6 weeks
500	33	14	500	58	26
1000	26	17	1000	37	6
2000	26	12	2000	62	18

The median duration of response, defined as improvement of resolution of clinical signs and symptoms, was 2 to 6 weeks.

Since the study was not designed to determine the benefit of monotherapy beyond 12 weeks, the

duration of response may be underestimated for the 25 to 33% of patients who continued to show clinical response after 12 weeks.

Survival. Median survival time from study entry (Study 500) was 249 days at the 500 mg b.i.d. dose compared to 215 days with the 1000 mg b.i.d. dose. However, during the first 12 weeks of therapy, there were 2 deaths in 53 patients in the 500 mg b.i.d. group versus 13 deaths in 51 patients in the 1000 mg b.i.d. group. The reason for this apparent mortality difference is not known. Survival in the two groups was similar beyond 12 weeks. The median survival times for these dosages were similar to recent historical controls with MAC when treated with combination therapies.

Median survival time from study entry in Study 577 was 199 days for the 500 mg b.i.d. dose and 179 days for the 1000 mg b.i.d. dose. During the first four weeks of therapy, while patients were maintained on their originally assigned dose, there were 11 deaths in 255 patients taking 500 mg b.i.d. and 18 deaths in 214 patients taking 1000 mg b.i.d.

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 Tablets, USP, Film-Coated

Pharmacokinetics for clarithromycin and 14-OH-clarithromycin metabolite was 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. Cmax occurred at 1.00 and 1.77 (mg/L) and Tmax were 1.5 and 2.2 hrs, respectively for the 250 mg and 500 mg (see **Table 18,** and **Figures 2 and 3**).

Table 18 **Mean (± SD) Pharmacokinetic Parameters for Clarithromycin Administered** **as a Single Dose in the Absence of Food**		
	Clarithromycin Dose	
Variable	**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] $AUC_{0\text{-}14\ hr}$

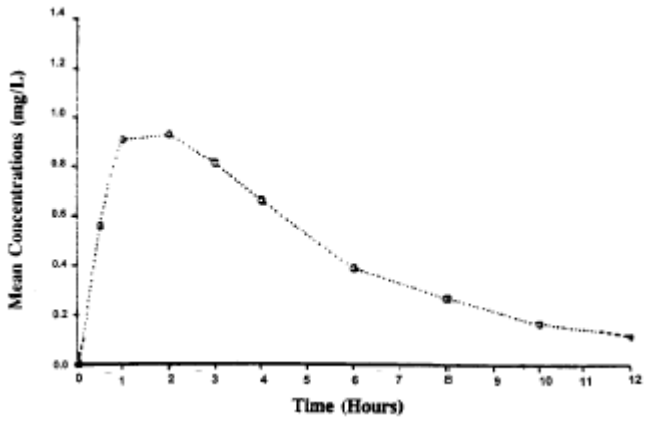


Figure 2: Plasma Clarithromycin Concentration (mg/mL) vs Time Following Oral Administration of a Single Dose of Clarithromyicn 250 mg

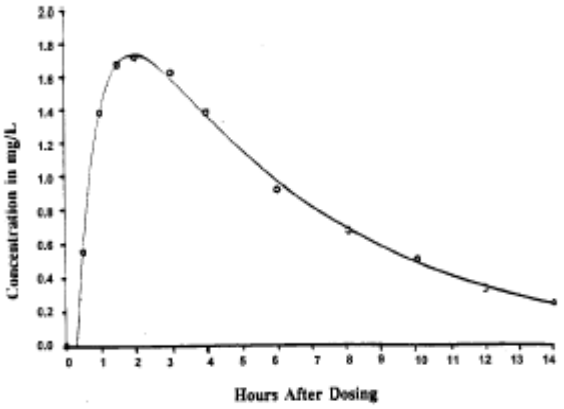


Figure 3: Plasma Clarithromycin Concentration (mg/L) vs Time Following Oral Administration of a Single Dose of Clarithromycin 500 mg

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 b.i.d. are listed in **Table 19**.

Table 19
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
$T_{½}$ (hr)	2.7	4.2	3.5	4.7
AUC_{0-12} (mg·h/L)	4.27 ± 1.52	4.91 ± 1.12	6.34 ± 1.82	4.72 ± 1.29

Clari., clarithromycin; 14-OH, 14-OH-clarithromycin

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 b.i.d.

The mean plasma concentration-time along the predicted curves for clarithromycin and 14-OH-clarithromycin metabolite are shown in **Figure 4.**

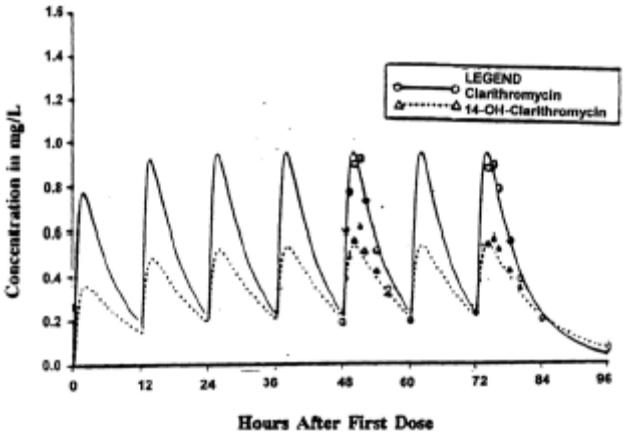


Figure 4: Mean Plasma Concentrations of Clarithromycin and 14-OH Clarithromycin vs Time Following Seven 250 mg B.I.D. Oral Doses of Clarithromycin

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 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.

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 **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

MICROBIOLOGY

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

Clarithromycin is active *in vitro* against various aerobic and anaerobic gram-positive and

gram-negative organisms as well as most MAC microorganisms. The in vitro activity of clarithromycin is presented in **Table 20**.

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

The ranges of MICs of clarithromycin, 14-OH-clarithromycin metabolite and the MICs required to inhibit 50% (MIC50) and 90% (MIC90) of bacterial are presented in **Tables 21and 22**. Beta-lactamase production should not have any effect on clarithromycin activity.

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

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

Table 20
***In Vitro* Susceptibility* of Strains**
of Gram-Positive and Gram-Negative Bacteria to Clarithromycin

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

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

Table 21
***In vitro* Susceptibility of Different Bacteria to Clarithromycin**

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

Table 22
***In vitro* Susceptibility of Different Bacteria to 14-OH-Clarithromycin**

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

Susceptibility Testing excluding Mycobacteria

Dilution Techniques

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

The standard single disc susceptibility test (using the 15 mcg clarithromycin disc) and the dilution susceptibility test should be interpreted according to the criteria in **Table 23.**

Table 23
Criteria for the Interpretation of Standard Single Disc and Dilution Susceptibility Tests except for *H. influenzae*

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

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

The standard single disc susceptibility test (using the 15 mcg clarithromycin disc) for *H. Influenzae* should be interpreted according to the criteria in **Table 24**.

Table 24
Criteria for the Interpretation of Standard Single Disc and Dilution Susceptibility Tests for *H. influenzae*

	Zone Diameter (mm)	Appropriate MIC Correlate (mg/L)
Susceptible	≥ 13	≤ 8
Intermediate*	11 - 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 procedure44 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 23**.

Standardized Dilution Techniques

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin powder should provide the following MIC values for *S. aureus* and *H. influenzae* (see **Table 25**).

Table 25
Standard Clarithromycin Powder MIC Values

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

Standardized Diffusion Techniques

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15-mcg clarithromycin disk should provide the following zone diameters for S. aureus and H. influenzae (see **Table 26**).

Table 26
Zone Diameter for the 15 mcg Clarithromycin Disc

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

In vitro Activity of Clarithromycin against Mycobacteria

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

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

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

Clarithromycin activity was evaluated against Mycobacterium tuberculosis microorganisms. In 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 Tablets, USP, Film-Coated)

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 27**).

Table 27 Acute LD_{50} values of Clarithromycin			
Species	**Sex**	**Route**	**LD_{50} value (g/kg)**
Mice	M	p.o.	2.74
	F	p.o.	2.7
	M	s.c.	>5.0
	F	s.c.	>5.0
	M	i.p.	1.03
	F	i.p.	0.85
	M	i.v.	0.17
	F	i.v.	0.2
Rats	M	p.o.	3.47
	F	p.o.	2.7
	M	s.c.	>5.0
	F	s.c.	>5.0
	M	i.p.	6.69
	F	i.p.	7.58

The primary signs of toxicity included reduction in activities, behaviours, 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 Tablets, USP, Film-Coated

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 two 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 one month with oral doses of 0, 25, 100 or 400 mg/kg/day. Two animals out of ten 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 intra-ocular 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 to 14.3 mg/kg/day (70 kg person).

Chronic Toxicity

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 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 also 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 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 one 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 to160 mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after 150 mg/kg/day were 2 times the human serum levels.

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

In rabbits, *in utero* fetal loss occurred at an intravenous dose of 33 mg/ 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: CONSUMER INFORMATION

[Pr]GEN-CLARITHROMYCIN
clarithromycin tablets, USP, film-coated

This leaflet is part III of a three-part "Product Monograph" published when GEN-CLARITHROMYCIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about GEN-CLARITHROMYCIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

GEN-CLARITHROMYCIN is used to treat certain infections caused by bacteria, such as pneumonia, bronchitis, infections of the sinuses, skin, and throat.

It can also be prescribed to prevent and combat MAC disease in patients with HIV. MAC is a short word for *Mycobacterium avium* complex, the germs that cause MAC disease.

What it does:

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

When it should not be used:

Do not take GEN-CLARITHROMYCIN if you have ever had an allergic reaction to it, or if you are sensitive to it or erythromycin, or other antibacterial agents of the same family or to any ingredient in the formulation (see **What the important nonmedicinal ingredients are:**).

Do not take GEN-CLARITHROMYCIN if you are taking astemizole*, cisapride*, pimozide, terfenadine*, ergotamine, or dihydroergotamine. These medicines can interact, possibly leading to a irregular heartbeat pattern; deaths have occurred.

* no longer marketed in Canada.

What the medicinal ingredient is:

The medicinal ingredient is clarithromycin.

What the important nonmedicinal ingredients are:

Colloidal silicon dioxide, croscarmellose sodium, D&C yellow No. 10 aluminum lake, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, propylene glycol, stearic acid, titanium dioxide and vanillin.

What dosage forms it comes in:

250 mg and 500 mg strengths come as immediate-release film-coated tablets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

GEN-CLARITHROMYCIN should not be used in pregnancy unless advised by your doctor due to potential hazards to the fetus. Do not take GEN-CLARITHROMYCIN without first talking to your doctor if you are breast-feeding a baby.

Before taking GEN-CLARITHROMYCIN, tell your doctor if you have liver or kidney disease. You may not be able to take clarithromycin, or you may require a lower dose and special monitoring during therapy. Talk to your doctor if GEN-CLARITHROMYCIN gives you prolonged and severe diarrhea.

The development of antibiotic resistance has been seen in patients with HIV receiving clarithromycin. To avoid failure of the treatment with a potential for developing antimicrobial resistance and a risk of failure with subsequent therapy, you/your child should follow closely the prescribed regimen.

BEFORE you use GEN-CLARITHROMYCIN talk to your doctor or pharmacist:

- about all health problems you have now or have had in the past;
- about all other medicines you are taking, including non-prescription medicines, nutritional supplements, or herbal products; (see **INTERACTIONS WITH THIS MEDICATION**)
- if you have or develop severe diarrhea as this may be a sign of a more serious condition;
- if you have kidney problems;
- if you have liver problems;
- if you are taking astemizole, terfenadine, cisapride, pimozide, ergotamine, dihydroergotamine, digoxin, or colchicine.
- if you have any unusual or allergic reaction (rash, difficulty of breathing) to clarithromycin or any of the nonmedicinal ingredients in GEN-CLARITHROMYCIN (see "What the important nonmedicinal ingredients are"), other medicines, foods, dyes, or preservatives;
- if you are pregnant, trying to get pregnant or are breast-feeding.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with GEN-CLARITHROMYCIN include:

Alaprazolam, alfentanil, astemizole/terfenadine, atorvastatin, bromocriptine, carbamazepine, cilostazol, cisapride/pimozide, colchicine, cyclosporine, digoxin, disopyramide/quinidine, ergotamine/dihydroergotamine, fluconazole, hexobarbital, lansoprazole/omeprazole, lovastatin/simvastatin, methylprednisolone, midazolam/triazolam, phenytoin, rifabutin/rifampin, ritonavir/indinavir, sildenafil, tacrolimus,

theophylline, valproate, vinblastine, warfarin/acenocoumarol, zidovudine and drugs metabolized by cytochrome P450 system

PROPER USE OF THIS MEDICATION

Usual Adult Dose:

GEN-CLARITHROMYCIN may be taken with or without meals.

Respiratory Tract or Skin Infections:

The usual dosage of GEN-CLARITHROMYCIN is 250 mg to 500 mg every 12 hours for 7 to 14 days.

MAC disease:

The recommended dose of GEN-CLARITHROMYCIN for prevention and treatment of MAC disease is 500 mg every 12 hours.

Treatment of disseminated MAC infection (MAC infection spread through your whole body) in patients with HIV should continue for life if improvement of symptoms is observed.

Overdose:

Contact your doctor or pharmacist if you have taken more than the recommended dose. Symptoms of GEN-CLARITHROMYCIN overdose are abdominal pain, vomiting, nausea, and diarrhea.

Missed Dose:

If you miss a dose, take it as soon as you remember unless it is almost time for the next dose. In that case, skip the missed dose and take the next one as directed. Do not take double or extra doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, GEN-CLARITHROMYCIN can cause side effects. The majority of side effects observed in clinical trials with GEN-CLARITHROMYCIN were of a mild and transient nature.

The following adverse reactions were reported during the clinical studies with clarithromycin, the medicinal ingredient (occurring between 1% and 10% in clinical trials) or during post-marketing surveillance: abdominal pain, abnormal taste, diarrhea, ear disorder, flatulence, indigestion, headache, nausea, rash, vomiting. Talk to your doctor or pharmacist if any of these side effects persist or become bothersome.

Serious side effects from GEN-CLARITHROMYCIN are not common.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Allergic reactions*			✓
	Severe diarrhea		✓	
	Severe abdominal cramps		✓	
	Irregular heart beat			✓

*Allergic reactions, with symptoms such as itching, skin eruptions, rash, sore throat, fever, swelling, skin rash, itchiness, difficulty breathing, lightheadedness/dizziness.

This is not a complete list of side effects. For any unexpected effects while taking GEN-CLARITHROMYCIN, contact your doctor or pharmacist.

HOW TO STORE IT

Keep GEN-CLARITHROMYCIN and all other medicines out of reach of children.

Store at room temperature 15°C - 30°C, in a tightly closed container. Protect from light. Do not use beyond the expiration date.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

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