PRODUCT MONOGRAPH

[Pr] RIVA-CLARITHROMYCIN

(clarithromycin tablets, USP, film-coated)

250 mg and 500 mg

Antibiotic

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

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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	croscarmellose sodium, D&C Yellow No. 10, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, pregelatinized starch, silicon dioxide, talc, titanium dioxide and triacetin.

INDICATIONS AND CLINICAL USE

RIVA-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 beta-lactamase 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

RIVA-CLARITHROMYCIN 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).*

Eradication of *Helicobacter pylori*

RIVA-CLARITHROMYCIN in the presence of acid suppression (with omeprazole) with another antibiotic (amoxicillin) is indicated for the eradication of *Helicobacter pylori (H. Pylori)* that may result in decreased recurrence of duodenal ulcer in patients with active duodenal ulcers and who are *H. pylori* positive (see CLINICAL TRIALS).

(For additional information on the use of Riva-clarithromycin in triple therapy for the treatment of *H. pylori* infection and active duodenal ulcer recurrence, refer to the Hp-PAC* Product Monograph.)

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

RIVA-CLARITHROMYCIN (clarithromycin tablets, USP, film-coated) is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin or 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 arrhytmias (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 "antibiotic-associated 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.

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

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.

Antibiotic Resistance in Relation to *H. pylori* Eradication

***Triple and Dual Therapy with Omeprazole*. Among the 113 triple therapy recipients with pretreatment *H. pylori* isolates susceptible to clarithromycin, 2/102 patients (2%) developed resistance after treatment with omeprazole, clarithromycin, and amoxicillin. Among patients who received triple therapy, 6/108 (5.6%) patients had pretreatment *H. pylori* isolates resistant to clarithromycin. Of these 6 patients, 3 (50%) had *H. pylori* eradicated at follow-up, and 3 (50%) remained positive after treatment. In 5/113 (4.4%) patients, no susceptibility data for clarithromycin pretreatment were available. Twenty-six patients 26/104 (25%) with pretreatment isolates susceptible to clarithromycin developed resistance after treatment with omeprazole and clarithromycin. Development of clarithromycin resistance should be considered as a possible risk especially when less efficient treatment regimens are used.**

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). 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.

Pediatric *(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.

Geriatric (>65 years of age)Use

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 pharmaco-kinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The majority of side effects observed in clinical trials involving 3563 patients treated with clarithromycin were of a mild and transient nature. 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 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.

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****

Table 1 Patients with Respiratory Tract or Skin Infections - Clarithromycin Tablets	
System Organ Class	**Adverse Reaction/Adverse Event***
Psychiatric disorders	**Nervousness** **Anxiety** **Insomnia** **Nightmare** **Depression** **Confusional state** **Disorientation** **Depersonalisation** **Hallucination** **Psychotic disorder**
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		
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 **Blood urea increased**	**1%** **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 Tables 6 and 7).

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 × 10^9/L**	**2%**	**2%**	**4%**
	White blood cell count decreased	**<1 × 10^9/L**	**0%**	**2%**	**0%**
	Blood urea increased	**>50 mg/dL**	**<1%**	**<1%**	**4%**

ULN = Upper Limit of Normal.

Patients with *H. Pylori* Infection - Triple Therapy
(clarithromycin/omeprazole/amoxicillin)

Adverse Reactions

A summary of drug-related adverse event incidence rates is presented in Table 7.

(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).

Table 7 Summary of Drug-Related Adverse Event Incidence Rates by System Organ Class		
	Patients With Drug-Related Adverse Events (% of Patients Treated)*	
System Organ Class	Omeprazole + Clarithromycin + Amoxicillin (n=137)	Omeprazole + Clarithromycin (n=130)
Gastrointestinal disorders	24 (18%)	21 (16%)
General disorders and administration site conditions	5 (4%)	0 (0%)
Nervous system disorders	15 (11%)	30 (23%)
Cardiac disorders	0 (0%)	1 (1%)
Investigations	9 (7%)	0 (0%)
Infections and infestations	1 (1%)	1(1%)
Hepatobiliary disorders	2(1%)	0 (0%)
Psychiatric disorders	1(1%)	1(1%)
Ear and labyrinth disorders	1(1%)	2 (2%)
Respiratory, thoracic and mediastinal disorders	1(1%)	0 (0%)
Skin and subcutaneous tissue disorders	3 (2%)	1 (1%)
Eye disorders	0 (0%)	1 (1%)
Reproductive system and breast disorders	1 (1%)	0 (0%)

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

Note: There is a statistical difference (Fisher's exact two-sided, p-value = 0.009) between omeprazole + clarithromycin + amoxicillin (11%) versus omeprazole + clarithromycin (23%) in regard to nervous system disorders.

Patients with *H. Pylori* Infection - Dual Therapy (clarithromycin/omeprazole)

Adverse Reactions

Of 346 patients, 156 (45%) reported at least one adverse event. Adverse events associated with the Gastrointestinal disorders, Nervous system disorders, and Infections and infestations system organ class (SOC) were the most commonly reported adverse events among clarithromycin/omeprazole-treated patients. One hundred and two patients (29%) reported gastrointestinal disorder events. The most common adverse events reported in the Gastroinstestinal disorder SOC were nausea (5%) diarrhea (4%), vomiting (3%), and abdominal pain (3%). Eighty-three patients (24%) reported adverse events in the Nervous system disorders SOC. Dysgeusia (15%), headache (5%), and dizziness (2%) were the most frequently reported events in the Nervous system disorders SOC. Twenty-nine patients (8%) reported adverse events in the Infections and infestations SOC. Infection (3%) was the most frequently reported adverse event in the Infections and infestations SOC. Adverse events by system organ class for all patients treated with clarithromycin and omeprazole are presented in Table 8.

(*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).

Table 8
Summary of Adverse Event Incidence by System Organ Class
all Patients Treated with Clarithromycin/Omeprazole

System Organ Class*	Number (%) of Patients (N=346)
Infections and infestations	29 (8%)
Neoplasma benign, malignant and unspecified	2 (<1%)
Metabolism and nutrition disorders	1 (<1%)
Psychiatric disorders	12 (3%)
Nervous system disorders	83 (24%)
Eye disorders	2 (<1%)
Ear and labyrinth disorders	1 (<1%)
Cardiac disorders	6 (2%)
Vascular disorders	1 (<1%)
Respiratory, thoracic and mediastinal disorders	5 (1%)
Gastrointestinal disorders	102 (29%)
Hepatobiliary disorders	1 (<1%)
Skin and subcutaneous tissue disorders	11 (3%)
Musculoskeletal and connective tissue disorders	12 (3%)
Renal and urinary disorders	2 (<1%)
General disorders and administration site conditions	24 (7%)
Investigations	8 (2%)
Injury, poisoning and procedural complications	3 (1%)
TOTAL**	156 (45%)

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

The most commonly reported adverse events for the 346 patients who received clarithromycin and omeprazole were: taste perversion (15%), nausea (5%), headache (5%), diarrhea (4%), vomiting (3%), abdominal pain (3%), and infection (3%).

Table 9 presents adverse events reported by 1% or more of clarithromycin/omeprazole-treated patients.

Table 9 Rank-Order of Adverse Events for Patients who Received Clarithromycin and Omeprazole		
System Organ Class	**Adverse Event***	**Number (%) of Patients**
Nervous system disorders	**Dysgeusia**	**53 (15%)**
	Headache	**16 (5%)**
	Dizziness	**7 (2%)**
Gastrointestinal disorders	**Nausea.**	**18 (5%)**
	Diarrhea	**15 (4%)**
	Vomiting	**12 (3%)**
	Abdominal Pain	**11 (3%)**
	Tongue Discoloration	**8 (2%)**
	Constipation	**5 (1%)**
	Dry Mouth	**4 (1%)**
Infections and infestations	**Infection**	**9 (3%)**
	Rhinitis	**7 (2%)**
	Pharyngitis	**5 (1%)**
General disorders and administration site conditions	**Pain**	**6 (2%)**
	Asthenia	**4 (1%)**
	Chills	**4 (1%)**
	Influenza	**4 (1%)**
Musculoskelatal and connective tissue disorders	**Back Pain**	**5 (1%)**
Skin and subcutaneous tissue disorders	**Rash**	**4 (1%)**
* **Events reported in at least 1% of the clarithromycin/omeprazole population.**		

Twelve (4%) of the clarithromycin/omeprazole-treated patients prematurely discontinued from study drug therapy due to adverse events. The most frequently reported adverse events leading to withdrawal included taste perversion, nausea, and headache. Three patients treated with clarithromycin and omeprazole died during follow-up periods; none of the deaths were considered by the investigator to be related to study drug administration.

Few laboratory abnormalities were observed among clarithromycin/ omeprazole-treated patients. The incidence of possibly clinically significant hematology and serum chemistry variables was < 1% for any variable evaluated.

<u>Post-Market Adverse Drug Reactions</u>

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

formulations.

Table 10 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

Table 10 Post-Market Adverse Drug Reactions	
System Organ Class	**Adverse Event**
Immune system disorders	**Anaphylaxis**
Ear and labyrinth disorders	**Tinnitus**
	Hearing loss
Renal and urinary disorders	**Interstitial nephritis**

DRUG INTERACTIONS

Serious Drug Interactions

1. **Concomitant administration of clarithromycin with astemizole, cisapride, pimozide, terfenadine, ergotamine, or dihydroergotamine is contraindicated (see CONTRAINDICATIONS and DRUG INTERACTIONS).**
2. **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 11. 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 11 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 colchicine toxicity (see PRECAUTIONS: General and ADVERSE REACTIONS)**

Table 11 Established or Potential Drug-Drug Interactions			
Clarithromycin	**Ref**	**Effect**	**Clinical Comments**
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 11 Established or Potential Drug-Drug Interactions			
Clarithromycin	**Ref**	**Effect**	**Clinical Comments**
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** **↑ omeprazole C_{max} & AUC_{0-24}** **↑ levels of clarithromycin**	**One study demonstrated that concomitant administration of clarithromycin and lansoprazole resulted in mild changes of serum concentrations of lansoprazole and 14-OH clarithromycin. However, no dosage adjustment is considered necessary based on these data.** **Clarithromycin 500 mg 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.** **To a lesser extent, omeprazole administration increases the serum concentrations of clarithromycin. Omeprazole administration also increases tissue and mucus concentrations of clarithromycin.**
Lovastatin / Simvastatin **Atorvastatin**	**C** **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.** **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 11 Established or Potential Drug-Drug Interactions			
Clarithromycin	**Ref**	**Effect**	**Clinical Comments**
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 11 Established or Potential Drug-Drug Interactions			
Clarithromycin	**Ref**	**Effect**	**Clinical Comments**
Theophylline	**P**	**Potential ↑ in theophylline concentrations**	**Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations.** **Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range.**
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.**			

Combination Therapy with Omeprazole and/or Amoxicillin

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

Drug-Food Interactions

RIVA-CLARITHROMYCIN (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

RIVA-CLARITHROMYCIN (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).

Recommended Dose and Dosage Adjustment

Adults with Respiratory Tract or Skin Infections

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

Table 12 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 RIVA-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.

Eradication of *Helicobacter pylori*

***Triple Therapy:* RIVA-CLARITHROMYCIN/omeprazole/amoxicillin**

The recommended dose is RIVA-CLARITHROMYCIN 500 mg b.i.d. in conjunction with amoxicillin 1 g b.i.d. and omeprazole 20 mg daily for 10 days (see CLINICAL TRIALS).

For more information on omeprazole or amoxicillin, refer to their respective Product Monographs, under DOSAGE AND ADMINISTRATION.

(FOR ADDITIONAL INFORMATION ON THE USE OF RIVA-CLARITHROMYCIN IN TRIPLE THERAPY FOR THE TREATMENT OF *H. PYLORI* INFECTION AND ACTIVE

DUODENAL ULCER RECURRENCE, REFER TO THE HP-PAC* PRODUCT MONOGRAPH.)

Dual Therapy: **RIVA-CLARITHROMYCIN*/omeprazole***

In patients who are sensitive to penicillin-based therapy (e.g. amoxicillin), dual therapy with clarithromycin and omeprazole may provide a feasible alternative.

The recommended dose is clarithromycin 500 mg t.i.d plus omeprazole 40 mg q.d. for 14 days, followed by 20 mg omeprazole q.d. for 14 days (see CLINICAL TRIALS).

Optimal therapeutic regimens consisting of a shorter treatment duration for the eradication of *H. pylori* are yet to be determined.

Adults with Mycobacterial Infections

Prophylaxis

The recommended dose of RIVA-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

RIVA-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.

Pharmacodynamics

Eradication of *Helicobacter pylori*

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

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

Pharmacokinetics

A summary of clarithromycin pharmacokinetic parameters following the administration of clarithromycin film-coated tablets is provided in Table 13. For details see DETAILED PHARMACOLOGY in PART II of the Product Monograph.

Table 13 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 40 & 41)** **** Multiple doses (from Table 41)**				

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, Clarithromycin tablets 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.

***Clarithromycin and omeprazole*. Clarithromycin 500 mg t.i.d. and omeprazole 40 mg q.d. were studied in fasting healthy adult subjects. When clarithromycin was given alone as 500 mg q8h, the mean steady state C_{max} value was approximately 3.8 mcg/mL and the mean C_{min} value was approximately 1.8 mcg/mL. The mean AUC_{0-8} for clarithromycin was 22.9 mcg·hr/mL. The T_{max} and half life were 2.1 hrs and 5.3 hrs, respectively, when clarithromycin was dosed at 500 mg t.i.d. When clarithromycin was administered with omeprazole, increases in omeprazole half-life and AUC_{0-24} were observed. For all subjects combined, the mean omeprazole AUC_{0-24} was 89% greater and the harmonic mean for omeprazole t½ was 34% greater when omeprazole was administered with clarithromycin than when omeprazole was administered alone. When clarithromycin was administered with omeprazole, the steady state C_{max}, C_{min}, and AUC_{0-8} of clarithromycin were increased by 10%, 27%, and 15%, respectively over values achieved when clarithromycin was administered with placebo.**

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 14.

Table 14
Representative Clarithromycin Tissue and Serum Concentrations Following the Administration of 250 mg b.i.d of Clarithromycin Film-Coated Tablets

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

**** in vitro* data.**

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.

<u>Special Populations and Conditions</u>

Pediatrics

Use of clarithromycin tablets in children under 12 years of age has not been studied.

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 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

Store film-coated tablets between 15 and 25°C in a tightly closed container. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Riva-Clarithromycin 250 mg: Oval, yellow film-coated debossed with "P" logo on one side and "250" on the other side. Available in HDPE bottles of 100 and 250 tablets.

Riva-Clarithromycin 500 mg: Oval, yellow film-coated debossed with "P" logo on one side and "500" on the other side. Available in HDPE bottles of 100 and 250 tablets.

Composition :

Riva-Clarithromycin 250 mg contains 250 mg of clarithromycin for oral administration. Non-Medicinal Ingredients: Croscarmellose Sodium, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polydextrose, Polyethylene Glycol, Povidone, Pregelatinized Starch, Quinoline Yellow WS (D&C Yellow No. 10), Silicon Dioxide Colloidal, Talc, Titanium Dioxide and Triacetin. RIVA-CLARITHROMYCIN tablets does not contain Tartrazine.

Riva-Clarithromycin 500 mg contains 500 mg of clarithromycin for oral administration. Non-Medicinal Ingredients: Croscarmellose Sodium, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polydextrose, Polyethylene Glycol, Povidone, Pregelatinized Starch, Quinoline Yellow WS (D&C Yellow No. 10), Silicon Dioxide Colloidal, Talc, Titanium Dioxide and Triacetin. RIVA-CLARITHROMYCIN tablets does not contain Tartrazine.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

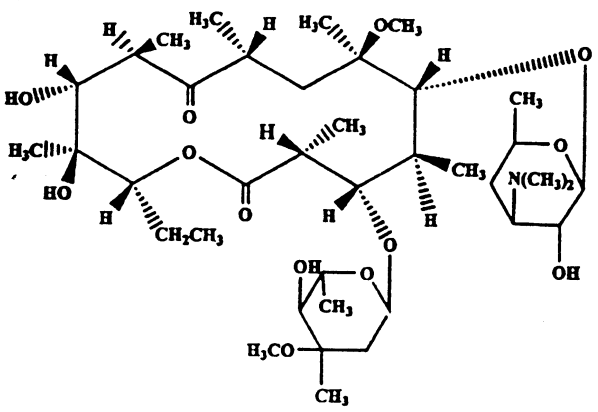
Proper Name: **Clarithromycin**

Chemical Name: **(3R*,4S*, 5S*, 6R*, 7R*, 9R*, 11R*, 12R*, 13S*, 14R*)-4-[(2,6-dideoxy-3-C-methyl-3-0-methyl-alpha-L-ribo-hexopyranosyl)oxy]-14-ethyl-12,13-dihydroxy-7-methoxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-beta-D-xylo-hexopyranosyl]oxy]-oxacyclotetradecane-2-10-dione.**

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

Molecular mass: **747.96**

Structural Formula:



Physicochemical properties:

Clarithromycin is a white to off-white crystalline powder. It is slightly soluble in methanol, ethanol and acetonitrile, and practically insoluble in water. The pKa of clarithromycin is 8.48; the pH of a 0.2% (Methanol:Water, 5:95) slurry is 8.8.

The partition coefficient of clarithromycin is influenced by the pH of the water phase and polarity of the organic phase. For octanol (dipole moment = 0.25): water, the partition 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

Mycobacterial Infections

Prophylaxis

Table 15 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)**	**341341**	**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 16 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%**

Table 16 Summary of Efficacy Results in Immunocompromised Adult Patients Receiving Prophylaxis Against *M. avium* Complex					
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**	
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 hospitalized	**166/339 (49%)**	**189/330 (57%)**	**0.764 (0.610, 0.955)**	**0.018***	**- 23.6%**

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 17). 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/mm^3 (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.

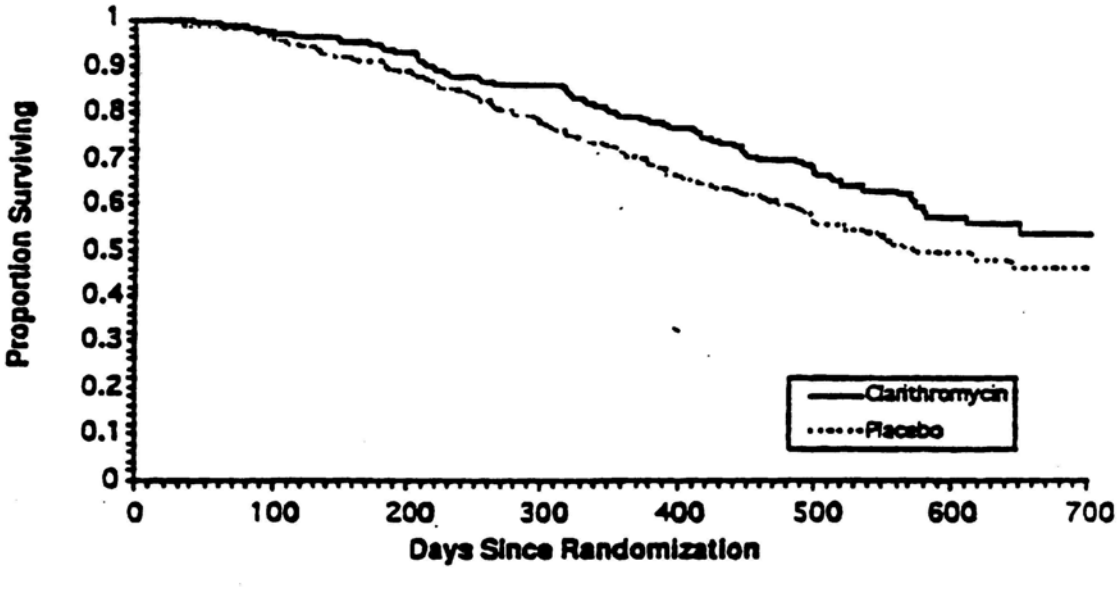


Figure 2 : Survival of All Randomized Immunocompromized Adult Patients Receiving Clarithromycin in Prophylaxis Against *M. avium* Complex or Placebo

Table 17
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

Two studies summarized in Table 18 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 18
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 19).**

Table 19
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 20.**

Table 20
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.

Eradication of *Helicobacter pylori* - Triple Therapy

Clarithromycin/omeprazole/amoxicillin

In a well controlled double-blind study, *Helicobacter pylori (H. pylori*) infected duodenal ulcer patients received triple therapy with clarithromycin 500 mg b.i.d., amoxicillin 1000 mg b.i.d. and omeprazole 20 mg daily for 10 days or dual therapy with clarithromycin 500 mg t.i.d. and omeprazole 40 mg daily for 14 days. *H. pylori* was eradicated in 90% of the patients receiving clarithromycin triple therapy and in 60% of the patients receiving dual therapy.

A summary of the Trial Design is presented in Table 21.

Table 21
Summary of the Trial Design
Efficacy of Clarithromycin in the Eradication of *Helicobacter pylori*—Triple Therapy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean Age (Range)
183	Phase III, randomized, double-blind, multicenter	*Treatment 1* Clarithromycin 500 mg b.i.d. with Amoxicillin 1 000 mg b.i.d. and Omeprazole 20 mg QD *Treatment 2* Clarithromycin 500 mg b.i.d. with Omeprazole 40 mg QD oral *Treatment 1*: 10 days *Treatment 2*: 14 days	267 patients	18 - 75 years

The ulcer healing rates and corresponding 95% confidence intervals are presented in Table 22.

Table 22
Ulcer Healing [95% C.I.] at Four to Six Weeks Follow-up

Patient Subset	Clarithromycin + Omeprazole + Amoxicillin	Clarithromycin + Omeprazole	p-value
Clinically Evaluable	93% (118/127) [87.0, 96.7]	91% (104/114) [84.5, 95.7]	0.641
Intent-to-Treat #1	93% (122/131) [87.4, 96.8]	92% (111/121) [85.3, 96.0]	0.812
Intent-to-Treat #2	90% (122/136) [83.3, 94.3]	85% (111/130) [78.1, 91.0]	0.353

- **An ulcer was defined as a circumscribed break in the duodenal mucosa that measured 5 to 25 mm in the longest diameter with apparent depth and was covered with an exudate.**
- **Duodenal ulcer was identified by endoscopy and *H. pylori* infection at baseline was defined as at least two of three positive tests from ^{13}C UBT, CLOtest®, histology and culture.**
- ***H. pylori* eradication at 4 to 6 weeks posttreatment was defined as at least two of three negative tests from ^{13}C UBT gastric biopsy for culture, histology and CLOtest®.**

Intent-to-Treat #1: excluded patients with no confirmed evidence of *H. pylori* pretreatment, patients who had no duodenal ulcer pretreatment, and patients who did not return for a particular visit or did not have a particular procedure performed (e.g., endoscopy).

Intent-to-Treat #2: excluded patients with no confirmed evidence of *H. pylori* pretreatment and patients with no duodenal ulcer pretreatment, but included as failures patients who did not return for a particular visit or did not have a particular procedure performed (e.g., endoscopy).

The *H. pylori* eradication rates and corresponding 95% confidence intervals are summarized in Table 23.

For all patient subsets, triple therapy with clarithromycin, omeprazole, and amoxicillin achieved a statistically higher eradication rate than dual therapy ($p < 0.001$). These differences were also observed when the eradication rates were adjusted for potentially influential factors such as ulcer characteristics, age, and smoking. In addition, the eradication rates within each treatment group were similar for smokers and non-smokers.

Table 23
Global Eradication [95% C.I.] at Four- to Six-Week Follow-up

	Omeprazole + Clarithromycin + Amoxicillin	Omeprazole + Clarithromycin	p-value
Bacteriologically Evaluable	**91% (115/127) [84.1, 95.0]**	**59% (68/115) [49.6, 68.2]**	**<0.001**
Intent-to-Treat #1	**90% (120/133) [83.9, 94.7]**	**60% (72/120) [50.7, 68.8]**	**<0.001**
Intent-to-Treat #2	**88% (120/136) [81.6, 93.1]**	**55% (72/130) [46.4, 64.1]**	**<0.001**

- **An ulcer was defined as a circumscribed break in the duodenal mucosa that measured 5 to 25 mm in the longest diameter with apparent depth and was covered with an exudate.**
- **Duodenal ulcer was identified by endoscopy and *H. pylori* infection at baseline was defined as at least two of three positive tests from ^{13}C UBT, CLOtest®, histology and culture.**
- ***H. pylori* eradication at 4 to 6 weeks posttreatment was defined as at least two of three negative tests from ^{13}C UBT gastric biopsy for culture, histology and CLOtest®.**

Intent-to-Treat #1: excluded patients with no confirmed evidence of *H. pylori* pretreatment, patients who had no duodenal ulcer pretreatment, and patients who did not return for a particular visit or did not have a particular procedure performed (e.g., endoscopy).

Intent-to-Treat #2: excluded patients with no confirmed evidence of *H. pylori* pretreatment and patients with no duodenal ulcer pretreatment, but included as failures patients who did not return for a particular visit or did not have a particular procedure performed (e.g., endoscopy).

***International, randomized, double-blind, placebo-controlled study*. In an international, randomized, double-blind, placebo-controlled study involving more than 100 patients in each of six treatment groups, patients with proven duodenal ulcer disease were randomized to treatment twice daily for 1 week with omeprazole, 20 mg (O), plus either placebo (P) or combinations of two of the following antimicrobials: amoxicillin, 1g (A), clarithromycin, 250 mg or 500 mg (C250, C500), or metronidazole, 400 mg (M). *H. pylori* eradication rates for the "all-patients-treated" analysis were 96% (OAC500), 95% (OMC250), 90% (OMC500), 84% (OAC250), 79% (OAM), and 1% (OP).**

***Independent, open, and non-randomized study*. In an independent, open, and non-randomized study, *H. pylori* infected patients received eradication therapy with clarithromycin 500 mg b.i.d. in conjunction with amoxicillin 1000 mg b.i.d. and omeprazole 20 mg q.d. (Group A) or omeprazole 20 mg b.i.d. (Group B) for 7 days. In those patients not previously treated with anti-*H. pylori* therapy, *H. pylori* was eradicated in 88% of patients in Group A and 86% of patients in Group B.**
(For additional information on the use of Clarithromycin in triple therapy for the treatment of *H. pylori* infection and active duodenal ulcer recurrence, refer to the Hp-PAC* Product Monograph).

Eradication of *H. pylori* - Dual Therapy

Clarithromycin/omeprazole

***H. pylori* is strongly associated with peptic ulcer disease. Ninety to 100% of patients with duodenal ulcers are infected with this pathogen. Eradication of *H. pylori* has been shown to reduce the rate of duodenal ulcer recurrence, thereby reducing the need for maintenance anti-secretory therapy.**

In four well controlled, double-blind studies, *H. pylori* infected duodenal ulcer patients received eradication therapy with clarithromycin 500 mg t.i.d. and omeprazole 40 mg daily for fourteen days followed by omeprazole 40 mg (study A) or omeprazole 20 mg (studies B, C and D) daily for an additional 14 days; patients in each control group received omeprazole alone for 28 days.

European Studies

A summary of the Trial Design is presented in Table 24.

Table 24
Summary of the Trial Design
Efficacy of Clarithromycin in the Eradication of Helicobacter pylori—Dual Therapy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)
A	Phase III, randomized, controlled, double-blind, multicenter study	*Treatment (1)*: Clarithromycin 500 mg t.i.d + omeprazole 40 mg q.d. for 14 days, followed by omeprazole 40 mg q.d. for 14 days.	*H. pylori* infected duodenal ulcer patients (n=69)*
		Treatment (2): Placebo (no clarithromycin) + omeprazole 40 mg q.d. for 14 days, followed by omeprazole 40 mg q.d. for 14 days.	*H. pylori* infected duodenal ulcer patients (n=75)*

*** Number of evaluable patients as per Table 25.**

Results of Study A are displayed in Table 25.

Table 25
Study A: Efficacy of Clarithromycin in the Eradication of Helicobacter pylori—Dual Therapy

Results	Treatment (1) Clarithromycin + Omeprazole*	Treatment (2) Omeprazole*	Statistical Significance
Ulcer Healing Rates at Post-Treatment	100% (65/65)	99% (72/73)	> 0.999
Ulcer Prevalence Rate 6-Month Follow-up Visit 12-Month Follow-Up Visit	 4% (2/53) 4% (2/48)	 54% (37/69) 78% (49/63)	 < 0.001 < 0.001
H. pylori Global Eradication Rate 4 to 6-Week Follow-up Visit	83% (57/69)	1% (1/75)	< 0.001

* For details of treatment see Table 24

A summary of the Trial Design is presented in Table 26.

Table 26
Summary of the Trial Design
Efficacy of Clarithromycin in the Eradication of *Helicobacter pylori* - Dual Therapy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)
B	Phase III, randomized, controlled, double-blind, multicenter study	*Treatment (1)*: Clarithromycin 500 mg t.i.d + omeprazole 40 mg q.d. for 14 days, followed by omeprazole 20 mg q.d. for 14 days.	*H. pylori* infected duodenal ulcer patients (n=93)*
		Treatment (2): Placebo (no clarithromycin) + omeprazole 40 mg q.d. for 14 days, followed by omeprazole 20 mg q.d. for 14 days.	*H. pylori* infected duodenal ulcer patients (n=96)*

* Number of evaluable patients as per Table 27.

Results of Study B are displayed in Table 27.

Table 27
Study B: Efficacy of Clarithromycin in the Eradication of *Helicobacter pylori* - Dual Therapy

Results	Treatment (1) Clarithromycin + Omeprazole*	Treatment (2) Omeprazole*	Statistical Significance
Ulcer Healing Rates at Post-Treatment	99% (86/87)	95% (84/88)	0.368
Ulcer Prevalence Rate 6-Month Follow-up Visit 12-Month Follow-Up Visit	 11% (9/79) N/A	 52% (45/86) N/A	 < 0.001 N/A
H. pylori Global Eradication Rate 4 to 6-Week Follow-up Visit	74% (69/93)	4% (4/96)	< 0.001

N/A No information available.
* For details of treatment see Table 28

North American Studies

A summary of the Trial Design is presented in Table 28.

Table 28
Summary of Demographics and Trial Design
Efficacy of Clarithromycin in the Eradication of *Helicobacter pylori* - Dual Therapy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)
C	Controlled, double-blind study	*Treatment (1)*: Clarithromycin 500 mg t.i.d. + omeprazole 40 mg q.d. for 14 days, followed by 20 mg omeprazole q.d. for 14 days.	*H. pylori* infected duodenal ulcer patients (n=69)*
		Treatment (2): Clarithromycin 500 mg t.i.d. for 14 days + placebo q.d. (no omeprazole) for 28 days.	*H. pylori* infected duodenal ulcer patients (n=70)*
		Treatment (3): Placebo t.i.d. (no clarithromycin) + omeprazole 40 mg q.d. (14 days), followed by omeprazole 20 mg q.d. (14 days).	*H. pylori* infected duodenal ulcer patients (n=65)*

* Number of evaluable patients as per Table 29.

Results of the Study C are displayed in Table 29.

Table 29
Study C: Efficacy of Clarithromycin in the Eradication of *Helicobacter pylori* - Dual Therapy

Results	Treatment (1) Clarithromycin + Omeprazole	Treatment (2) Clarithromycin	Treatment (3) Omeprazole	Treatment (1) *vs* Treatment (2) p-value	Treatment (1) *vs* Treatment (3) p-value
Ulcer Healing Rates at Post-Treatment	87% (60/69)	63% (44/70)	85% (55/65)	0.002	0.806
Ulcer Prevalence Rate 6-Month Follow-up Visit	53% (30/57)	65% (44/68)	72% (41/57)	0.203	0.053
H. pylori Global Eradication Rate 4 to 6-Wk Follow-up Visit 3-Month Follow-up Visit	 74% (43/58) 77% (37/48)	 34% (15/44) 37% (13/35)	 0% (0/55) 3% (1/38)	 < 0.001 < 0.001	 < 0.001 < 0.001

A summary of the Trial Design is presented in Table 30.

Table 30
Summary of Demographics and Trial Design
Efficacy of Clarithromycin in the Eradication of Helicobacter pylori—Dual Therapy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)
D	Controlled, double-blind study	*Treatment (1)*: Clarithromycin 500 mg t.i.d + omeprazole 40 mg q.d. for 14 days, followed by 20 mg omeprazole q.d. for 14 days.	*H. pylori* infected duodenal ulcer patients (n=82)*
		Treatment (2): Clarithromycin 500 mg t.i.d. for 14 days + placebo q.d. (no omeprazole) for 28 days.	*H. pylori* infected duodenal ulcer patients (n=86)*
		Treatment (3): Placebo t.i.d. (no clarithromycin) + omeprazole 40 mg q.d. (14 days), followed by omeprazole 20 mg q.d. (14 days).	*H. pylori* infected duodenal ulcer patients (n=88)*

*** Number of enrolled patients**

Results of the Study D are displayed in Table 31.

Table 31
Study D: Efficacy of Clarithromycin in the Eradication of Helicobacter pylori—Dual Therapy

Results	Treatment (1) Clarithromycin + Omeprazole	Treatment (2) Clarithromycin	Treatment (3) Omeprazole	Treatment (1) *vs* Treatment (2) p-value	Treatment (1) *vs* Treatment (3) p-value
Ulcer Healing Rates at Post-Treatment	94% (60/64)	71% (50/70)	89% (62/70)	<0.001	0.371
Ulcer Prevalence Rate 6-Month Follow-up Visit	30% (18/60)	49% (32/65)	76% (50/66)	0.031	<0.001
H. pylori Global Eradication Rate 4 to 6-Wk Follow-up Visit 3-Month Follow-up Visit	 64% (41/64) 72% (41/57)	 38% (18/48) 40% (19/48)	 0% (0/62) 0% (0/44)	 0.007 0.001	 < 0.001 < 0.001

Overall summary

In study A, *H. pylori* was eradicated in over 80% of patients who received clarithromycin and omeprazole and in only 1% of patients receiving omeprazole alone. In studies B, C, and D, the combined eradication rate was over 70% in patients receiving clarithromycin and omeprazole and less than 1% in patients receiving omeprazole alone. In each study, the rate of ulcer recurrence at 6 months was statistically lower in the clarithromycin and omeprazole treated patients when compared to patients receiving omeprazole alone.

Comparative Bioavailability Studies

A comparative bioavailability study of RIVA-CLARITHROMYCIN 500 mg tablets was performed. Pharmacokinetic and bioavailability data were measured in 40 volunteers in the *fasting* and *fed* states. The results are summarized in tables 32 and 33:

Table 32 - SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA SINGLE-DOSE, RANDOMIZED, 2-WAY, FASTING STUDY CLARITHROMYCIN (1 x 500 mg) From Measured Data

PARAMETER	GEOMETRIC MEAN ARITHMETIC MEAN (CV%)		RATIO (%) OF GEOMETRIC MEANS
	RIVA-Clarithromycin Tablets 500 mg	Biaxin®* BID Tablets 500 mg	
AUC_{0-T} (ng.h/mL)	17265.0 19190.1 (54.0)	16936.1 18733.4 (47.3)	101.94
$AUC_{0-\infty}$ (ng.h/mL)	17890.0 19943.7 (55.2)	17869.9 19729.0 (47.0)	100.11
C_{max} (ng/mL)	2201.8 2417.5 (46.2)	2125.4 2381.2 (47.9)	103.6
T_{max}* (h)	2.28 (31.2)	2.03 (31.1)	- - - - -
$T_{1/2}$** (h)	4.85 (20.1)	5.33 (41.0)	- - - - -

* Abbott Laboratories Inc., (Saint Laurent, Quebec) purchased in Canada.

** Expressed as arithmetic mean (CV%) only.

Conclusion

The objective of the present study was to determine the bioequivalence between Laboratoire Riva's clarithromycin 500 mg tablets and BIAXIN® 500 mg tablets under fasting conditions. The relative mean C_{max} of the Test to the Reference formulation was within 80 to 125% for both the measured and the potency-corrected data. Furthermore, the 90% confidence intervals of the relative mean AUC_T of the Test to Reference formulation were within the acceptance range of 80 to 125% for both the measured and the potency-corrected data.

Therefore, the Test formulation (Clarithromycin 500 mg tablets, Laboratoire Riva Inc., Québec, Canada) is judged to be bioequivalent to the Reference formulation (BIAXIN® Tablets 500 mg, Abbott Laboratories, Limited, Québec, Canada) on the basis of C_{max} and AUC parameters.

Table 33 - SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA SINGLE-DOSE, RANDOMIZED, 2-WAY, FED STUDY CLARITHROMYCIN (1 x 500 mg) From Measured Data

PARAMETER	GEOMETRIC MEAN ARITHMETIC MEAN (CV%)		RATIO (%) OF GEOMETRIC MEANS
	RIVA-Clarithromycin Tablets 500 mg	Biaxin®* BID Tablets 500 mg	
AUC_{0-T} (ng.h/mL)	11897.6 13030.7 (40.6)	12809.2 13513.3 (31.7)	92.88
$AUC_{0-\infty}$ (ng.h/mL)	12259.3 13381.4 (40.2)	13181.9 13881.9 (31.3)	93
C_{max} (ng/mL)	2009.0 2180.1 (38.1)	2154.3 2310.0 (34.0)	93.25
T_{max}* (h)	1.50 (21.1)	1.50 (46.4)	- - - - -
$T_{1/2}$** (h)	4.36 (16.5)	4.37 (17.5)	- - - - -

* Abbott Laboratories Inc., (Saint Laurent, Quebec) purchased in Canada.
** Expressed as arithmetic mean (CV%) only.

Conclusion

The objective of the present study was to determine the bioequivalence between Laboratoire Riva's clarithromycin 500 mg tablets and BIAXIN® 500 mg tablets under fed conditions. The relative geometric mean of the Test to the Reference formulation for C_{max} was within 80 to 125% for both the measured and the potency-corrected data. Furthermore, the 90% confidence interval of the relative geometric mean of the Test to the Reference formulation for AUC_T was within the acceptance range of 80 to 125% for both the measured and the potency-corrected data.

Therefore, the Test formulation (Clarithromycin 500 mg tablets, Laboratoire Riva Inc., Québec, Canada) is judged to be bioequivalent to the Reference formulation (BIAXIN® Tablets 500 mg, Abbott Laboratories, Limited, Québec, Canada) on the basis of C_{max} and AUC parameters.

DETAILED PHARMACOLOGY

General

Helicobacter pylori

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

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

Gustavson *et al.* (1995) showed that concentrations of 39.3, 23.1 mcg/g and 25.2 mcg/g clarithromycin were achieved in the gastric mucosa 2, 4, and 6 hours respectively after administering 500 mg clarithromycin t.i.d. and that corresponding concentrations of the 14 hydroxy-metabolite were 3.2, 1.1, and 4.1 mcg/g respectively. Similar results were obtained whether or not clarithromycin was given alone or together with 40 mg omeprazole once daily (Logan *et al*., 1995)[39]. Although the activity of the hydroxy metabolite is about half of the parent drug and its concentrations are lower, it may still contribute antibacterial activity.

Pharmacokinetics

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

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

Single Dose

Plasma levels were determined in 20 subjects following oral administration of a single-dose of 250 mg or 500 mg of clarithromycin under fasting conditions. C_{max} occurred at 1.00 and 1.77 (mg/L) and T_{max} were 1.5 and 2.2 hours, respectively for the 250 mg and 500 mg. (see Table 34, Figures 3 and 4).

Table 34
Mean (± SD) pharmacokinetic parameters for clarithromycin administered as a single dose in the absence of food

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

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

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

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

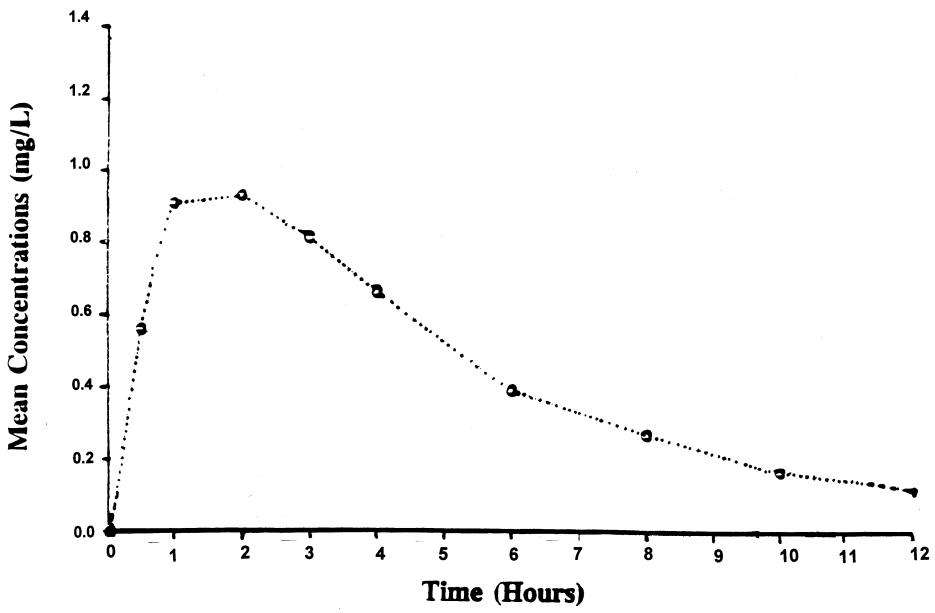


Figure 3: Plasma Clarithromycin Concentration (mg/mL) *vs* Time Following Oral Administration of a Single Dose of Clarithromycin 250mg

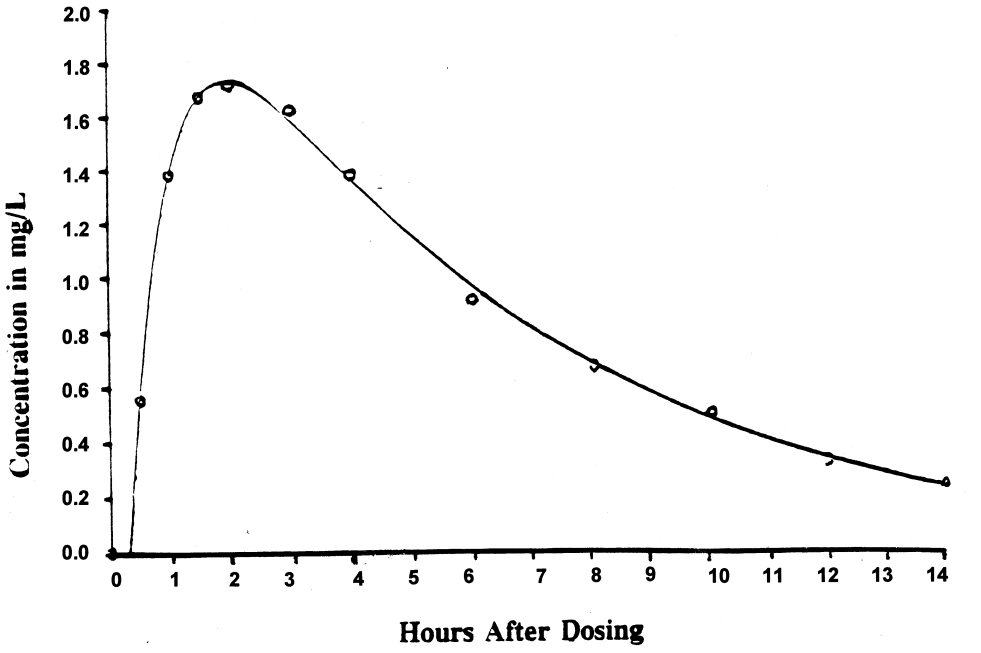


Figure 4: Plasma Clarithromycin Concentration (mg/mL) *vs* Time Following Oral Administration of a Single Dose of Clarithromycin 500mg

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 35.

Table 35
Representative estimated single and multiple dose pharmacokinetic parameters for clarithromycin and 14-OH clarithromycin

Variables	Single Dose		Multiple Dose after 5th Dose	
	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} (hr•mg/L)	4.27 ± 1.52	4.91 ± 1.12	6.34 ± 1.82	4.72 ± 1.29

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 5.

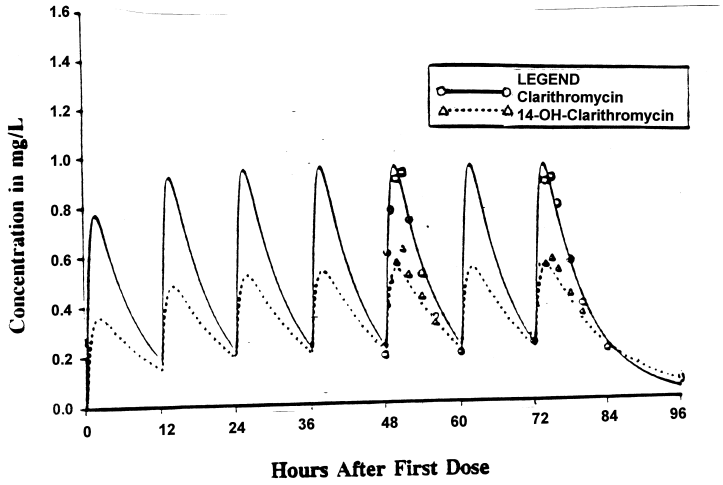


Figure 5: Mean Plasma Concentrations of Clarithromycin and 14-OH Clarithromycin *vs* Time Following Seven 250 mg B.I.D. Oral Doses of Clarithromycin

At 250 mg twice daily, approximately 20% of an orally administered dose is excreted in the urine as the unchanged parent drug. The urinary excretion of unchanged clarithromycin is somewhat greater (approximately 30%) with 500 mg twice daily dosing. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH-clarithromycin which accounts for an additional 10-15% of the dose with twice daily dosing at either 250 mg or 500 mg.

Most of the remainder of the dose is eliminated in the feces, primarily via the bile. About 5-10% 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).

Clarithromycin and Omeprazole

A pharmacokinetic study was conducted with clarithromycin 500 mg t.i.d. and omeprazole 40 mg q.d. When clarithromycin was given alone at 500 mg q8h, the mean steady-state C_{max} value was approximately 31% higher and the mean C_{min} value was approximately 119% higher than when clarithromycin is compared with a previous study at 500 mg q12h. The mean AUC_{0-24} for clarithromycin was 65% greater when 500 mg clarithromycin was given q8h rather than q12h. Neither T_{max} nor half-life values appeared substantially different between the q8h and q12h regimens.

When clarithromycin was administered with omeprazole, increases in omeprazole half-life and AUC_{0-24} were observed. For all subjects combined, the mean omeprazole AUC_{0-24} was 89% greater and the harmonic mean for omeprazole T½ was 34% greater when omeprazole was administered with clarithromycin than when omeprazole was administered alone. When clarithromycin was administered with omeprazole, the steady state C_{max}, C_{min}, and AUC_{0-8} of clarithromycin were increased by 10%, 27%, and 15%, respectively over values achieved when clarithromycin was administered with placebo.

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

Clarithromycin distributes readily into body tissues and fluids, and provides tissue concentrations that are higher than serum concentrations. Examples from tissue and serum concentrations are presented in Table 36.

Table 36
Representative clarithromycin tissue and serum concentrations

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

* *in vitro* data

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 37.

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

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

The ranges of MICs of clarithromycin, 14-OH-clarithromycin metabolite and the MICs required to inhibit 50% (MIC_{50}) and 90% (MIC_{90}) of bacterial are presented in Tables 38 and 39. 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 37
***In Vitro* Susceptibility® of Strains**
of Gram-Positive and Gram-Negative Bacteria to Clarithromycin

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

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

Table 38

***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
Helicobacter pylori †	13	0.03-0.06	0.03	0.03

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

Table 39
***In vitro* Susceptibility of Different Bacteria to 14-OH-Clarithromycin**

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

Clarithromycin Kill Kinetics Against *Helicobacter pylori*

Figure 7 illustrates the kill kinetics of clarithromycin and 14-OH clarithromycin against *H. pylori* at 8 × MIC and at pH 8.0; and Figure 8 illustrates the kill kinetics of clarithromycin and amoxicillin against *H. pylori* at pH 6.5.

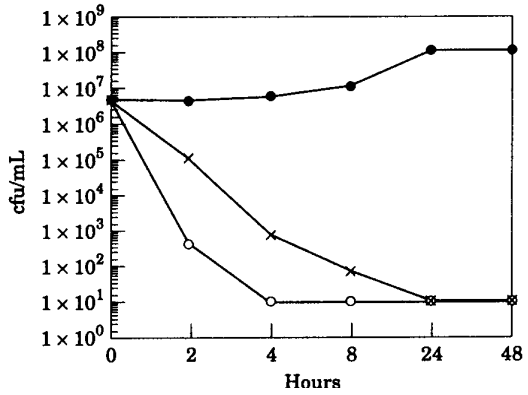


Figure 7: Kill kinetics of clarithromycin and 14-OH clarithromycin against *H. pylori* strain 2597 at 8 × MIC and at pH 8.0. A flask was inoculated to produce a starting inoculum of approximately 10^6 cfu/mL. The flask was then incubated in an anaerobe jar with CampyPak® and shaken gently at 37 ^{0}C. Counts were done at 0, 2, 4, 8, 24, and 48 h in physiological saline after 72 h incubation. ●, No antimicrobial; ○, clarithromycin (0.12 mg/L); x, 14-OH clarithromycin (0.24 mg/L).

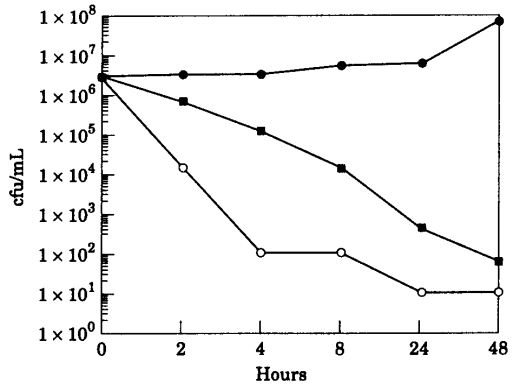


Figure 8: Kill kinetics of clarithromycin and amoxicillin against *H. pylori* strain 2597 at pH 6.5. Counts were done at 0, 2, 4, 8, 24, and 48 h in physiological saline after 72 h incubation. ●, No antimicrobial; ○, clarithromycin (3 mg/L); ■, amoxicillin (3 mg/L)

Susceptibility Testing excluding Mycobacteria and Helicobacter

Dilution Techniques

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

The standard single disc susceptibility test (using the 15 mcg clarithromycin disc) and the dilution susceptibility test should be interpreted according to the criteria in Table 40.

Table 40
Criteria for the Interpretation of Standard Single Disc and Dilution Susceptibility Tests except for *H. influenzae* and *H. pylori*

	Zone Diameter (mm)	Appropriate MIC Correlate (mg/L)
Susceptible	≥18	≤2
Intermediate*	14 - 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 41.

Table 41
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.

<u>Diffusion Techniques</u>

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

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15-mcg clarithromycin disk should be interpreted according to the criteria in Table 45.

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 42).

Table 42
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 43).

Table 43
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.

In vitro* Activity of Clarithromycin against *Helicobacter pylori

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

Susceptibility Test for *Helicobacter pylori*

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

clarithromycin plus omeprazole clinical trials fell into a distinct bimodal distribution of susceptible and resistant clarithromycin MICs.

If the broth microdilution MIC methodology published in Hachem CY *et al*., 1996 is used and the following tentative breakpoints are employed, there should be reasonable correlation between MIC results and clinical and microbiological outcomes for patients treated with clarithromycin plus omeprazole (see Table 44).

Table 44
Susceptibility Testing for *Helicobacter pylori* in Patients Treated with Clarithromycin and Omeprazole

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

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

TOXICOLOGY

Acute Toxicity

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 - > 5.0 g/kg. Acute toxicity did not differ markedly between sexes (Table 45).

Table 45 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

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 - 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 (20-27/sex/group) at dosages of 0, 1-6, 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 (4-5/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 (5-6/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.

<u>Mutagenicity</u>

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 150-160 mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after 150 mg/kg/day were 2 times the human serum levels.

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

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

Special Studies

Acute Renal Toxicity

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

Hepatotoxicity

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

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

RIVA-CLARITHROMYCIN

clarithromycin tablets, USP, film coated

This leaflet is part III of a three-part "Product Monograph" published when RIVA-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 RIVA-CLARITHROMYCIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

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

When used with other medications, it can treat infection caused by a bacteria called *H. pylori.* and reduce the risk of duodenal ulcer recurrence. A duodenal ulcer is a sore on the lining of the duodenum, which is the beginning of the small intestine.

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:

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

When it should not be used:

Do not take RIVA-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 RIVA-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:

The nonmedicinal ingredients are the following: Croscarmellose Sodium, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polydextrose, Polyethylene Glycol, Povidone, Pregelatinized Starch, Quinoline Yellow WS (D&C Yellow No. 10), Silicon Dioxide Colloidal, Talc, Titanium Dioxide and Triacetin. RIVA-CLARITHROMYCIN tablets does not contain Tartrazine.

What dosage forms it comes in:

This medicine comes in tablets (RIVA-CLARITHROMYCIN, 250 mg and 500 mg).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

Before taking RIVA-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 RIVA-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 RIVA-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 RIVA-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 RIVA-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:

RIVA-CLARITHROMYCIN may be taken with or without meals.

Respiratory Tract or Skin Infections:

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

Infections with *H. Pylori:*

***Triple Therapy*: RIVA-CLARITHROMYCIN + Omeprazole +Amoxillin The recommended dose is the following for 10 days:**
- **RIVA-CLARITHROMYCIN: 500 mg every 12 hours**
- **Omeprazole: 20 mg once daily**
- **Amoxicillin: 1 g every 12 hours**

***Double Therapy*: RIVA-CLARITHROMYCIN + Omeprazole The recommended dose is the following for 14 days:**
- **RIVA-CLARITHROMYCIN: 500 mg every 8 hours**
- **Omeprazole: 40 mg once daily**

followed by 20 mg omeprazole once daily for 14 days

MAC disease:

The recommended dose of RIVA-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 RIVA-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, RIVA-CLARITHROMYCIN can cause side effects. The majority of side effects observed in clinical trials with clarithromycin were of a mild and transient nature.

The following adverse reactions were reported during the clinical studies with clarithromycin, the medicinal ingredient (occuring 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 RIVA-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 RIVA-CLARITHROMYCIN, contact your doctor or pharmacist.

HOW TO STORE IT

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

Store between 15° and 25°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

This document plus the full product monograph, prepared for health professionals can be obtained by contacting:
Laboratoire Riva Inc. at: 1-800-363-7988

This leaflet was prepared by Laboratoire Riva Inc.å

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