SUMMARY OF PRODUCT CHARACTERISTICS

ACEM - 250 / 500

(Clarithromycin Tablets 250 / 500 mg USP)

Table of Contents

1. NAME OF THE MEDICAL PRODUCT 3
2. QUALITATIVE AND QUANTITATIVE COMPOSITION 3
3. PHARMACEUTICAL FORM 3
4. CLINICAL PARTICULARS 3
4.1 Therapeutic Indications 3
4.2 Posology and method of administration 4
4.3 Contraindications 4
4.4 Special warnings and precautions for use 4
4.5 Interaction with other medicinal products and other forms of Interaction 6
4.6 Pregnancy and Lactation 9
4.7 Effects on ability to drive and use machines 10
4.8 Undesirable Effects 10
4.9 Overdose 10
5. PHARMACOLOGICAL PROPERTIES 11
5.1 Pharmacodynamic properties: 11
5.2 Pharmacokinetic properties: 34
5.3 Preclinical safety data 38
6. PHARMACEUTICAL PARTICULARS 39
6.1 List of excipient(s) 39
6.2 Incompatibilities 39
6.3 Shelf-life 39
6.4 Special precautions for storage 39
6.5 Nature and contents of container 40
6.6 Instructions for use and handling 40
7. MARKETING AUTHORISATION HOLDER 40
8. MARKETING AUTHORISATION NUMBER(S) 40
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION 40
10. DATE OF REVISION OF THE TEXT 40

1. NAME OF THE MEDICAL PRODUCT

ACEM-250

ACEM-500

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACEM-250

Each film coated tablet contains:

Clarithromycin USP 250 mg

Colour used: Titanium dioxide & Lake of Quinoline Yellow

ACEM-500

Each film coated tablet contains:

Clarithromycin USP 500 mg

Colour used: Titanium dioxide & Lake of Quinoline Yellow

3. PHARMACEUTICAL FORM

Oral tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Pharyngitis
- Tonsillitis
- Sinusitis
- Chronic bronchitis
- Skin and soft tissue infections
- Urinary tract infections
- Disseminated or localized mycobacterial infections
- Legionella & Chlamydial infections

4.2 Posology and method of administration

The usual dosage is 250-500 mg twice daily by mouth for 7-14 days, depending upon the severity of infections.

Clarithromycin tablets may be given with or without food.

Infection	Dosage (q12h)	Normal Duration (days)
Pharyngitis/Tonsillitis	250 mg	10
Acute maxillary sinusitis	500 mg	14
Acute exacerbation of chronic bronchitis due to:		
S. pneumoniae	250 mg	7 to 14
M. catarrhalis	250 mg	7 to 14
H. influenzae	500 mg	7 to 14
Pneumonia due to:		
S. pneumoniae	250 mg	7 to 14
M. pneumoniae	250 mg	7 to 14
Uncomplicated skin and skin structure	250 mg	7 to 14

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Clarithromycin at a dose of 500 mg has been successfully used in triple therapies to treat H. pylori infection.

4.3 Contraindications

Hypersensitivity to macrolide antibiotics or any of the components of the formulation.

4.4 Special warnings and precautions for use

Warnings:

Clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus. Clarithromycin has demonstrated adverse effects of pregnancy outcome and/or embryo-fetal development in

monkeys, rats, mice, and rabbits at doses that produced plasma levels 2 to 17 times the serum levels achieved in humans treated at the maximum recommended human doses.
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, 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.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium 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 clinically effective against Clostridium difficile colitis.

Precautions:
General - Clarithromycin is principally excreted via the liver and kidney. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.
Clarithromycin in combination with ranitidine bismuth citrate therapy is not recommended in patients with creatinine clearance less than 25 ml/min.
Clarithromycin in combination with ranitidine bismuth citrate should not be used in patients with a history of acute porphyria.

4.5 Interaction with other medicinal products and other forms of Interaction

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. In two studies in which theophylline was administered with clarithromycin (a theophylline sustained-release formulation was dosed at either 6.5 mg/kg or 12 mg/kg together with 250 or 500 mg q12h clarithromycin), the steady-state levels of Cmax, Cmin, and the area under the serum concentration time curve (AUC) of theophylline increased about 20%.

Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered.

When clarithromycin and terfenadine were coadministered, plasma concentrations of the active acid metabolite of terfenadine were threefold higher, on average, than the values observed when terfenadine was administered alone. The pharmacokinetics of clarithromycin and the 14-hydroxy-clarithromycin were not significantly affected by coadministration of terfenadine once clarithromycin reached steady-state conditions. Concomitant administration of clarithromycin with terfenadine is contraindicated.

Clarithromycin 500 mg every 8 hours was given in combination with omeprazole 40 mg daily to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (Cmax, AUC0-24, and T½ increases of 30%, 89%, and 34%, respectively), by the 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.

Co-administration of clarithromycin with ranitidine bismuth citrate resulted in increased plasma ranitidine concentrations (57%), increased plasma bismuth trough concentrations

(48%), and increased 14-hydroxy-clarithromycin plasma concentrations (31%). These effects are clinically insignificant.

Simultaneous oral administration of clarithromycin and zidovudine to HIV-infected adult patients resulted in decreased steady-state zidovudine concentrations. When 500 mg of clarithromycin were administered twice daily, steady-state zidovudine AUC was reduced by a mean of 12% (n=4). Individual values ranged from a decrease of 34% to an increase of 14%. Based on limited data in 24 patients, when clarithromycin was administered two to four hours prior to oral zidovudine, the steady-state zidovudine Cmax was increased by approximately 2-fold, whereas the AUC was unaffected.

Simultaneous administration of clarithromycin and didanosine to 12 HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.

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 Cmin and AUC of 33% and 18%, respectively. Steady-state concentrations of 14-OH clarithromycin were not significantly affected by concomitant administration of fluconazole.

Concomitant administration of clarithromycin and ritonavir (n=22) resulted in a 77% increase in clarithromycin AUC and a 100% decrease in the AUC of 14-OH clarithromycin. Clarithromycin may be administered without dosage adjustment to patients with normal renal function taking ritonavir. However, for patients with renal impairment, the following dosage adjustments should be considered. For patients with CLCR 30 to 60 mg/min, the dose of clarithromycin should be reduced by 50%. For patients with CLCR < 30 ml/min, the dose of clarithromycin should be decreased by 75%.

Spontaneous reports in the post-marketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral

anticoagulants. Prothrombin times should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously.

Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post-marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin levels should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.
The following drug interactions, other than increased serum concentrations of carbamazepine and active acid metabolite of terfenadine, have not been reported in clinical trials with clarithromycin; however, they have been observed with erythromycin products and/or with clarithromycin in post-marketing experience.

Concurrent use of erythromycin or clarithromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Erythromycin has been reported to decrease the clearance of triazolam and, thus, may increase the pharmacologic effect of triazolam. There have been post-marketing reports of drug interactions and CNS effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam.

There have been reports of an interaction between erythromycin and astemizole resulting in QT prolongation and torsades de pointes. Concomitant administration of erythromycin and astemizole is contraindicated. Because clarithromycin is also metabolized by cytochrome P450, concomitant administration of clarithromycin with astemizole is not recommended.

As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g., lovastatin and simvastatin), through inhibition of cytochrome P450 metabolism of these drugs. Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

The use of erythromycin and clarithromycin in patients concurrently taking drugs metabolized by the cytochrome P450 system may be associated with elevations in serum levels of these other drugs. There have been reports of interactions of erythromycin and/or clarithromycin with carbamazepine, cyclosporine, tacrolimus, hexobarbital, phenytoin, alfentanil, disopyramide, lovastatin, bromocriptine, valproate, terfenadine, cisapride, pimozide, rifabutin, and astemizole. Serum concentrations of drugs metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving these drugs.

4.6 Pregnancy and Lactation

Pregnancy

Pregnancy, Teratogenic Effects, Pregnancy Category C

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 (approximately 2 times the recommended maximum human dose based on mg/m2) 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 (2 and 4 times the recommended maximum human dose based on mg/m2, respectively) 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 (an approximate equidose of the recommended maximum human dose based on mg/m2) produced fetal growth retardation at plasma levels that were 2 times the human serum levels.

There are no adequate and well-controlled studies in pregnant women. Clarithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether clarithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when clarithromycin is administered to a nursing woman. It is known that clarithromycin is excreted in the milk of lactating animals and that other drugs of this class are 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable Effects

Nausea, vomiting, dyspepsia, diarrhea, abdominal pain, headache and taste disturbance. Transient CNS symptoms like anxiety, dizziness, insomnia, confusion.

4.9 Overdose

There is no information on overdosage with clarithromycin.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

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

Clarithromycin is active in vitro against a variety of aerobic and anaerobic gram-positive and gram-negative microorganisms as well as most Mycobacterium avium complex (MAC) microorganisms.

Additionally, the 14-OH clarithromycin metabolite also has clinically significant antimicrobial activity. The 14-OH clarithromycin is twice as active against Haemophilus influenzae microorganisms as the parent compound. However, for Mycobacterium avium complex (MAC) isolates the 14-OH metabolite is 4 to 7 times less active than clarithromycin. The clinical significance of this activity against Mycobacterium avium complex is unknown.

Clarithromycin has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections.

Aerobic Gram-positive Microorganisms: *Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyrogenes.*

Aerobic Gram-negative Microorganisms: *Haemophilus influenzae, Moraxella catarrhalis.*

Other Microorganisms: *Mycoplasma pneumoniae, Chlamydia pneumoniae (TWAR).*

Mycobacteria*: Mycobacterium avium complex (MAC) consisting of: Mycobacterium avium, Mycobacterium intracellulare.*

Beta-lactamase production should have no effect on clarithromycin activity.

Omeprazole/clarithromycin dual therapy; ranitidine bismuth citrate / clarithromycin dual therapy; omeprazole / clarithromycin / amoxicillin triple therapy; and lansoprazole / clarithromycin / amoxicillin triple therapy have been shown to be active against most strains of Helicobacter pylori in vitro and in clinical infections.

Helicobacter: *Helicobacter pylori.*

Pretreatment Resistance

Clarithromycin pretreatment resistance rates were 3.5% (4/113) in the omeprazole/clarithromycin dual-therapy studies (M93-067, M93-100) and 9.3% (41/439) in the omeprazole/clarithromycin/amoxicillin triple-therapy studies (126, 127, M96-446). Clarithromycin pretreatment resistance was 12.6% (44/348) in the ranitidine bismuth citrate/clarithromycin bid versus tid clinical study (H2BA3001). Clarithromycin pretreatment resistance rates were 9.5% (91/960) by E-test and 11.3% (12/106) by agar dilution in the lansoprazole/clarithromycin/amoxicillin triple therapy clinical trials (M93-125, M93-130, M93-131, M95-392, and M95-399).

Amoxicillin pretreatment susceptible isolates (<0.25 mg/ml) were found in 99.3% (436/439) of the patients in the omeprazole/clarithromycin/amoxicillin clinical studies (126, 127, M96-446). Amoxicillin pretreatment minimum inhibitory concentrations (MICs) >0.25 mg/ml occurred in 0.7% (3/439) of the patients, all of whom were in the clarithromycin/amoxicillin study arm. Amoxicillin pretreatment susceptible isolates (<0.25 mg/ml) occurred in 97.8% (936/957) and 98.0% (98/100) of the patients in the lansoprazole/clarithromycin/amoxicillin triple-therapy clinical trials by E-test and agar dilution, respectively. Twenty-one of the 957 patients (2.2%) by E-test and 2 of 100 patients (2.0%) by agar dilution had amoxicillin pretreatment MICs of >0.25 mg/ml. Two patients had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of >256 mg/ml by E-test.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes*						
Clarithromycin Pretreatment Results		**Clarithromycin Post-treatment Results**				
		***H. pylori* negative - eradicated**	***H. pylori* positive - not eradicated Post-treatment susceptibility results**			
			S†	**I†**	**R†**	**No MIC**
Omeprazole 40 mg qd/clarithromycin 500 mg tid for 14 days followed by omeprazole 20 mg qd for another 14 days (M93-067, M93-100)						
Susceptible†	108	72	1		26	9

Intermediate†	1				1	
Resistant†	4				4	
Ranitidine bismuth citrate 400 mg bid/clarithromycin 500 mg tid for 14 days followed by ranitidine bismuth citrate 400 mg bid for another 14 days (H2BA3001)						
Susceptible†	124	98	4		14	8
Intermediate†	3	2				1
Resistant[b]	17	1			15	1
Rantidine bismuth citrate 400 mg bid/clarithromycin 500 mg bid for 14 days followed by ranitidine bismuth citrate 400 mg bid for another 14 days (H2BA3001)						
Susceptible†	125	106	1	1	12	5
Intermediate†	2	2				
Resistant†	20	1			19	
Omeprazole 20 mg bid/clarithromycin 500 mg bid/amoxicillin 1 g bid for 10 days (126, 127, M96-446)						
Susceptible†	171	153	7		3	8
Intermediate†						
Resistant†	14	4	1		6	3
Lansoprazole 30 mg bid/clarithromycin 500 mg bid/amoxicillin 1 g bid for 14 days (M95-399, M93-131, M95-392)						
Susceptible†	112	105				7
Intermediate†	3	3				
Resistant†	17	6			7	4
Lansoprazole 30 mg bid/clarithromycin 500 mg bid/amoxicillin 1 g bid for 10 days (M95-399)						
Susceptible†	42	40	1		1	
Intermediate†						
Resistant†	4	1			3	
* Includes only patients with pretreatment clarithromycin susceptibility tests.						
† Susceptible (S) MIC <0.25 µg/ml, Intermediate (I) MIC 0.5-1.0 µg/ml, Resistant (R) MIC >2 µg/ml.						

Patients not eradicated of H. pylori following omeprazole / clarithromycin, ranitidine bismuth citrate / clarithromycin, omeprazole / clarithromycin / amoxicillin, or lansoprazole / clarithromycin / amoxicillin therapy would likely have clarithromycin resistant H. pylori isolates. Therefore, for patients who fail therapy, clarithromycin susceptibility testing should be done, if possible. Patients with clarithromycin resistant H. pylori should not be treated with any of the following: omeprazole / clarithromycin dual therapy; ranitidine bismuth citrate / clarithromycin dual therapy; omeprazole / clarithromycin / amoxicillin triple therapy; lansoprazole / clarithromycin / amoxicillin triple therapy; or other regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes

In the omeprazole / clarithromycin / amoxicillin triple-therapy clinical trials, 84.9% (157/185) of the patients who had pretreatment amoxicillin susceptible MICs (<0.25 mg/ml) were eradicated of H. pylori and 15.1% (28/185) failed therapy. Of the 28 patients who failed triple therapy, 11 had no post-treatment susceptibility test results, and 17 had post-treatment H. pylori isolates with amoxicillin susceptible MICs. Eleven of the patients who failed triple therapy also had post-treatment H. pylori isolates with clarithromycin resistant MICs.

Susceptibility Testing Excluding Mycobacteria and Helicobacter

Dilution Techniques: Quantitative methods are used to determine minimum 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 method1 (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of clarithromycin powder. The MIC values should be interpreted according to the criteria in the table below.

MIC (mcg/ml)	Interpretation
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.

A report of "Intermediate" indicates that the result should 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 the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation.
A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.
Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure2 requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15-µg clarithromycin to test the susceptibility of microorganisms to clarithromycin.

In Vitro Activity of Clarithromycin Against Mycobacteria
Clarithromycin has demonstrated in vitro activity against Mycobacterium avium complex (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 M. avium complex (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 media increases from 5.0 to 7.4.

At pH 7.4, MIC values determined with Mueller-Hinton agar were 4- to 8-fold higher than those observed with Middlebrook 7H12 media. Utilization of oleic acid-albumin-dextrose-catalase (OADC) in these assays has been shown to further alter MIC values.

Clarithromycin activity against 80 MAC isolates from AIDS patients and 211 MAC isolates from non-AIDS patients was evaluated using a microdilution method with Middlebrook 7H9 broth. Results showed an MIC value 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 was also shown to be active against phagocytized M. avium complex (MAC) in mouse and human macrophage cell cultures as well as in the beige mouse infection model.

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

Susceptibility Testing for Mycobacterium Avium Complex (MAC)

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 minimum inhibitory concentration (MIC) values against Mycobacterium avium complex (MAC) organisms have not been standardized or 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.

Susceptibility Test for Helicobacter pylori

The reference methodology for susceptibility testing of H. pylori is agar dilution MICs.3 One to three microliters of an inoculum equivalent to a No. 2 McFarland standard (1 ´ 107 -

1 ´ 108 CFU/ml for H. pylori) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (>2-weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for Campylobacter species. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the criteria shown in the tables below.

Clarithromycin MIC (µg/ml)*	**Interpretation**
<0.25	Susceptible (S)
0.5-1.0	Intermediate (I)
>2.0	Resistant (R)
* These are tentative breakpoints for the agar dilution methodology, and they should not be used to interpret results obtained using alternative methods.	

Amoxicillin MIC (µg/ml)*†	**Interpretation**
<0.25	Susceptible (S)
* These are tentative breakpoints for the agar dilution methodology, and they should not be used to interpret results obtained using alternative methods.	
† There were not enough organisms with MICs > 0.25 µg/ml to determine a resistance breakpoint.	

Animal Pharmacology

Clarithromycin is rapidly and well-absorbed with dose-linear kinetics, low protein binding, and a high volume of distribution. Plasma half-life ranged from 1-6 hours and was species dependent. High tissue concentrations were achieved, but negligible accumulation was observed. Fecal clearance predominated. Hepatotoxicity occurred in all species tested (i.e., in rats and monkeys at doses 2 times greater than and in dogs at doses comparable to the maximum human daily dose, based on mg/m2). Renal tubular degeneration (calculated on a mg/m2 basis) occurred in rats at doses 2 times, in monkeys at doses 8 times, and in dogs at doses 12 times greater than the maximum human daily dose. Testicular atrophy (on a

mg/m2 basis) occurred in rats at doses 7 times, in dogs at doses 3 times, and in monkeys at doses 8 times greater than the maximum human daily dose. Corneal opacity (on a mg/m2 basis) occurred in dogs at doses 12 times and in monkeys at doses 8 times greater than the maximum human daily dose. Lymphoid depletion (on a mg/m2 basis) occurred in dogs at doses 3 times greater than and in monkeys at doses 2 times greater than the maximum human daily dose. These adverse events were absent during clinical trials.

Clinical experience

Rev Esp Enferm Dig 2003 Mar;95(3):202-9

seven-day proton pump inhibitor, amoxicillin and clarithromycin triple therapy. factors that influence Helicobacter pylori eradications success.

Boixeda D, Martin De Argila C, Bermejo F, Lopez Sanroman A, Hernandez Ranz F, Garcia Plaza A

Servicio de Gaestroenterologia. Hospital Ramon y Cajal. Universidad de Alcala. Madrid, Spain.

[Medline record in process]

to underlying diseases, H. pylori eradication was achieved in 77.4% (74-80%) of peptic ulcers and 77% (71-82%) of functional dyspepsia (p=n.s.). With our two treatment regimens (OCA/PCA) eradication success was 74/81% in peptic ulcer (p=0.03), and 72/80% in functional dyspepsia (p=0.1). In the multivariate analysis, type of therapy was the only variable that correlated with eradication success (odds ratio 1.5; 95% CI: 1.1-2.1) (c2 model: 6,4; p=0.01). Conclusions: standard triple therapy containing a proton pump inhibitor, clarithromycin and amoxicillin for seven days achieves in our community a moderate eradication success; this result could improve by using pantoprazole instead of omeprazole. This therapy is equally effective in patients with peptic ulcer and functional dyspepsia.

Antibiot Khimioter 2002;47(9):18-21

[Evaluation of clarithromycin efficacy in the treatment of community-acquired pneumonia on the basis of the Binax NOW test results (a prospective open trial).]

[Article in Russian]

Guchev IA, Klochkov OI, Ul'ianov VA

Pulmonology Unit of Military Hospital, Smolensk.

The results of the treatment of community-acquired pneumonia with clarithromycin (500 mg bid for 6-8 days) at 172 patients (military recruits aged 18-25) are presented. Diagnosis, infection performance, treatment efficacy were evaluated by complex of data (X-ray, sputum analysis by bacteriological and cultural tests and immunochromatography test Binax NOW for pneumococcal antigen identification). High efficacy of clarithromycin for the treatment of moderate and mild pneumonia (including pneumococcal pneumonia) was demonstrated. Side effects were registered at 6.2 per cent of patients (gastro-intestinal disorders at 5 patients) and 1 general urticaria at 1 patient whose treatment had to be changed).

Scand J Gastroenterol 2002 Nov;37(11):1265-8

Seven-day triple therapy with omeprazole, amoxycillin and clarithromycin for Helicobacter pylori infection in haemodialysis patients.

Tsukada K, Miyazaki T, Katoh H, Masuda N, Ojima H, Fukai Y, Nakajima M, Manda R, Fukuchi M, Kuwano H, Tsukada O

Dept. of First Surgery, Gunma University School of Medicine, Ueda Kidney Clinic, Maebashi, Japan. katukada@topaz.ocn.ne.jp

BACKGROUND: Triple therapy is accepted as the treatment of choice for Helicobacter pylori eradication, but there is no consensus on how long the therapy should be maintained in haemodialysis (HD(+)) patients. Our aims in this study were to evaluate the safety and efficacy of the 7-day triple therapy in HD(+) patients. METHOD: Forty-seven HD(+) and 55 HD(-) patients with dyspepsia underwent endoscopy. The prevalence of H. pylori was detected by Giemsa stain, followed by the urea breath test (UBT). H. pylori(+) patients were scheduled to undergo 7-day triple therapy and the success of eradication was investigated by UBT. RESULTS: Forty-five (44%) patients were positive for H. pylori. Forty of them underwent triple therapy and 39 (98%) patients completed the treatment. Eradication was successful in 32 (82%) and unsuccessful in 7 (18%) patients. There was no significant difference between these groups in age, gender, endoscopic findings or HD, and only previous treatment was significant for eradication failure by univariate and multivariate logistic regression analysis. Side effects were observed in 2 (15%) of 13 HD(+) and 3 (11%) of 27 HD(-) patients, and one HD(-) patient had to stop medication because of severe nausea and vomiting. The eradication rate was 93% (28/30) in patients without previous treatment. The triple therapy was unsuccessful in 7 patients, and 4 of them again underwent 7-day triple therapy, but all resulted in failure. CONCLUSIONS: Seven-day triple therapy is safe and effective for primary treatment of H. pylori infection in both HD(+) and HD(-) patients, but a new treatment is necessary for patients with previous treatment.

Am J Gastroenterol 2002 Oct;97(10):2536-9

Comparison of azithromycin and clarithromycin in triple therapy regimens for the eradication of Helicobacter pylori.

Sullivan B, Coyle W, Nemec R, Dunteman T

Naval Medical Center Portsmouth, Virginia, USA.

OBJECTIVE: We sought to compare an azithromycin-based regimen with an already established clarithromycin-based regimen in the eradication of Helicobacter pylori infection. METHODS: A prospective, randomized, blinded comparative analysis was performed on 56 patients with upper GI symptoms who presented to the Gastroenterology Department at the Naval Medical Center Portsmouth. All patients had documented H. pylori infection on endoscopy via rapid urease test and histopathology. Patients were randomized to a treatment arm, which consisted of bismuth, clarithromycin, amoxicillin, and lansoprazole (B-LAC) or one consisting of bismuth, azithromycin, amoxicillin, and lansoprazole (B-LAA). To assess eradication, patients then received repeat endoscopy at 8 wk from entrance into the study. Rapid urease test and histopathology were again used to evaluate infection. Patients recorded all side effects. Comparison between the two groups was made using the chi2 method. RESULTS: Of the 56 patients included in the study, 27 went on to receive B-LAC, whereas 29 received B-LAA. The per protocol eradication rate was 84.6% with B-LAC and 55.5% with B-LAA ($p = 0.021$). Under intention to treat analysis, the eradication rates for B-LAC and B-LAA were 81% and 52%, respectively ($p = 0.019$). There was a significant difference between the two groups in number of subjects using nonsteroidal anti-inflammatory drugs (NSAIDs) ($p = 0.013$) and a trend toward a difference in histamine-2 (H2) blocker use ($p = 0.066$). Taking these two variables into account, a logistical regression was performed and continued to show a significant superiority in the B-LAC regimen ($p = 0.03$). CONCLUSIONS: The results of our study suggest that B-LAC is superior to B-LAA in the eradication of Helicobacter pylori. Our results also suggest that B-LAA is not a suitable regimen in the treatment of H. pylori because of its substandard eradication rate.

Clin Ther 2002 Sep;24(9):1414-25

Open-label, randomized comparison of the efficacy and tolerability of clarithromycin, levofloxacin, and cefuroxime axetil in the treatment of adults with acute bacterial exacerbations of chronic bronchitis.

Weiss LR

Department of Emergency Medicine, Knox Community Hospital, Mount Vernon, Ohio 43050, USA. Weiss@whiteflower.net

BACKGROUND: In the absence of a confirmed pathogen, empiric antimicrobial treatment of patients with acute exacerbations of chronic bronchitis and acute bacterial exacerbations of chronic bronchitis (ABECB) is accepted as standard practice and recommended in treatment guidelines. OBJECTIVE: This study compared the efficacy and tolerability of a 10-day course of 3 antimicrobial regimens commonly used to treat adults with ABECB. METHODS: This prospective, open-label, randomized study assessed clarithromycin 500 mg twice daily, levofloxacin 500 mg once daily, and cefuroxime axetil 250 mg twice daily, each administered for 10 days with food, in patients with ABECB. Efficacy was determined on the basis of the clinical response to treatment and need for hospitalization and/or further antimicrobial therapy. RESULTS: A total of 283 patients (150 men, 133 women) with a mean age of 55 years (range, 29 to 86 years) were randomized to receive clarithromycin (n = 97), levofloxacin (n = 94), or cefuroxime axetil (n = 92). Of 262 clinically assessable patients, clinical cure or improvement occurred in 87.9% (80/91) of those treated with clarithromycin, 87.4% (76/87) of those treated with levofloxacin, and 79.8% (67/84) of those treated with cefuroxime axetil. Eight (8.8%) clarithromycin-treated patients, 6 (6.9%) levofloxacin-treated patients, and 12 (14.3%) cefuroxime axetil-treated patients required a change in antimicrobial therapy to achieve clinical cure/improvement; between-group differences were not significant. No patients treated with clarithromycin required hospitalization for further antimicrobial treatment, compared with 3.4% (3/87) of levofloxacin-treated and 3.6% (3/84) of cefuroxime axetil-treated patients (P = NS). A total of 6.2% (6/97) of clarithromycin-treated patients were prematurely discontinued from treatment due to adverse events, compared with 7.4% (7/94) and 8.7% (8/92) of levofloxacin- and cefuroxime axetil-treated patients, respectively. CONCLUSION: A high rate of clinical efficacy and tolerability was observed in this population of patients with

ABECB treated with clarithromycin 500 mg twice daily, levofloxacin 500 mg once daily, or cefuroxime axetil 250 mg twice daily for 10 days.

Infez Med 2001 Dec;9(4):217-25

[Clarithromycin switch therapy in adult patients suffering from community-acquired lower respiratory tract infections (LRTIs) requiring hospitalisation.]

[Article in Italian]

Beghi G, Aiolfi S, Patruno V

U.O. Riabilitazione Respiratoria, P.O. "Santa Marta" Rivolta d'Adda, A.O. "Ospedale Maggiore" di Crema.

[Medline record in process]

39 subjects aged 53-85 years suffering from COPD, admitted to our Unit, were enrolled in our study: four patients were diagnosed as having CAP; 35 patients meet the criteria of COPD exacerbation. The enrolled patients had been receiving clarithromycin (CLA) 500 mg i.v. every 12 hours; switching to oral therapy was decided on the basis of Ramirez's criteria. The mean total duration (SD) of treatement with CLA was 9.56 (1.87) days. During the study, 2 patients dropped out because of the detection of malignant tumoral cells in the sputum in one case and admission to the Intensive Care Unit because of pulmonary thromboembolism in the other. The clinical assessment made 24-72 hours after the end of the treatment confirmed the clinical efficacy of CLA (cure + improvement) in 35 out of 37 evaluable patients (94.59%). At the first follow-up visit, clinical efficacy was confirmed in 34 patients (91.89%). At the long-term follow-up visit, performed 30-45 days after the end of the study, none of the 34 "cured" patients had relapsed. Local and systemic tolerability was excellent in all patients, and no side effect attributable to the drug was reported. Our experience with switched clarithromycin therapy in patients with LRTIs confirms the validity of this approach.

Circulation 2002 Apr 2;105(13):1555-60

Effect of 3 months of antimicrobial treatment with clarithromycin in acute non-q-wave coronary syndrome.

Sinisalo J, Mattila K, Valtonen V, Anttonen O, Juvonen J, Melin J, Vuorinen-Markkola H, Nieminen MS

Helsinki University Central Hospital, Department of Medicine, Division of Cardiology, Finland. juha.sinisalo@hus.fi

BACKGROUND: Coronary artery disease, an inflammatory disease, may be caused by infection. We investigated whether the antibiotic clarithromycin would reduce morbidity and mortality in patients with acute non-Q-wave coronary syndrome. METHODS AND RESULTS: Altogether, 148 patients with acute non-Q-wave infarction or unstable angina were randomly assigned to receive double-blind treatment with either clarithromycin or placebo for 3 months. The primary end point was a composite of death, myocardial infarction, or unstable angina during treatment; the secondary end point was occurrence of any cardiovascular event during the entire follow-up period (average 555 days, range 138 to 924 days). There was a trend toward fewer patients meeting primary end-point criteria in the clarithromycin group than in the placebo group (11 versus 19 patients, respectively; risk ratio 0.54, 95% CI 0.25 to 1.14; P=0.10). By the end of the entire follow-up, 16 patients in the clarithromycin group and 27 in the placebo group had experienced a cardiovascular event (risk ratio 0.49, 95% CI 0.26 to 0.92; P=0.03). CONCLUSIONS: Clarithromycin appears to reduce the risk of ischemic cardiovascular events in patients presenting with acute non-Q-wave infarction or unstable angina. No signs of this effect diminishing were observed during follow-up.

Pediatr Infect Dis J 2001 Dec;20(12):1149-54

Efficacy and safety of clarithromycin versus erythromycin for the treatment of pertussis: a prospective, randomized, single blind trial.

Lebel MH, Mehra S

Hopital Sainte-Justine, University of Montreal, Montreal, Canada. Marc_Lebel@SSSS.gouv.qc.ca

BACKGROUND: Pertussis is still a prevalent public health problem, and antibiotic therapy may decrease disease severity and limit communicability. Erythromycin is the recommended antibiotic for treatment and prophylaxis of pertussis; however, side effects of erythromycin limit its usefulness in some patients. Clarithromycin, a newer macrolide, has good in vitro activity against Bordetella pertussis and a better side effect profile. GOALS OF THE STUDY: To compare the microbiologic and clinical efficacy and the clinical safety of a 7-day course of clarithromycin vs. a 14-day course of erythromycin in children with pertussis. DESIGN: Prospective, randomized, single blind (investigator), parallel group trial. METHODS: Children from 1 month to 16 years of age presenting with a clinically defined pertussis syndrome were eligible for the study. After obtaining informed written consent, we randomized patients to receive either clarithromycin (7.5 mg/kg/dose twice a day for 7 days) or erythromycin (13.3 mg/kg/dose three times a day for 14 days). Nasopharyngeal cultures for B. pertussis were performed at enrollment and after end of treatment. Clinical assessments were performed at enrollment, at end of treatment and at a 1-month follow-up visit. Adverse event data were collected throughout the study. RESULTS: The clarithromycin (n = 76) and erythromycin (n = 77) groups were well-matched for age and previous pertussis immunization. Microbiologic eradication and clinical cure rates were 100% (31 of 31) for clarithromycin and 96% (22 of 23) for erythromycin. The clarithromycin group had significantly fewer adverse events [45% (34 of 76) for clarithromycin vs. 62% (48 of 77) for erythromycin; P = 0.035], and compliance with the medication regimen was significantly higher in these patients. CONCLUSIONS: A 7-day regimen of clarithromycin and a 14-day course of erythromycin were equally effective for treatment of pertussis. Clarithromycin was better tolerated than conventional erythromycin therapy.

Jpn J Antibiot 1989 Feb;42(2):304-22

[Basic and clinical studies on clarithromycin in pediatrics.]

[Article in Japanese]

Iwai N, Taneda Y, Miyazu M, Nakamura H, Kasai K

Department of Pediatrics, Meitetsu Hospital.

Clarithromycin (TE-031, A-56268) is a new macrolide antibiotic developed by Taisho Pharmaceutical Co., Ltd. Basic and clinical studies in the field of pediatrics were carried out on a granular preparation and 50 mg tablets of TE-031 designed for use in children. The following results were obtained. 1. Concentrations of TE-031 in the serum and its excretion in the urine were investigated in children. Six children were orally administered with a TE-031 granular preparation at 10 mg/kg in a cross-over study 30 minutes before meal and 30 minutes after meal. When the drug was ingested before meal, the mean peak serum concentration occurred 1 hour later and was 5.32 +/- 1.20 micrograms/ml. The mean half-life of TE-031 in the serum was 3.6 +/- 1.0 hours, and drug levels decreased to 1.94 +/- 0.55 micrograms/ml at 6 hours after dosing. In cases of the postprandial administration, the mean peak serum level was 4.21 +/- 1.25 micrograms/ml, occurring 2 hours after ingestion. The mean serum half-life in these cases was 3.5 +/- 1.3 hours, and serum levels decreased to 1.66 +/- 0.47 micrograms/ml at 6 hours after dosing. Mean urinary recovery rates during the initial 6 hours after ingestion were 30.5 +/- 6.4% in the cases of preprandial administration and 34.7 +/- 7.3% with postprandial administration. In addition, 30 minutes before meal, 50 mg tablets of TE-031 were orally administered to 3 children in a dose level equivalent to approximately 10 mg/kg, followed by monitoring of serum and urinary levels. It was found that the mean serum concentration showed a peak value of 4.10 +/- 0.44 micrograms/ml at 2 hours after dosing, the mean serum half-life was 3.5 +/- 0.7 hours, and the mean level fell to 1.90 +/- 0.55 micrograms/ml by 6 hours after dosing. The mean 6-hour urinary recovery rate was 32.7 +/- 12.1%. On the basis of the above results, it has been surmised that, in comparison to conventional macrolide antibiotics. TE-031 is better maintained in the blood at a high concentration and is more efficiently excreted into the urine. In addition, the data show that the bioavailability of TE-031 is slightly superior when the drug is administered on an empty stomach compared with after a meal. And finally, it was found that the granular and 50 mg tablet preparations of TE-031 are almost equivalent

in terms of the absorption and the excretion of the drug.(ABSTRACT TRUNCATED AT 400 WORDS)

Jpn J Antibiot 1989 Feb;42(2):401-10

[Clinical efficacy of clarithromycin in the field of pediatrics.]

[Article in Japanese]

Ogura H, Kubota H, Nomura I, Tomoda T, Araki K, Ogura Y, Kurashige T

Department of Pediatrics, Kochi Medical School.

A new macrolide antibiotic, clarithromycin (TE-031, A-56268), was studied for its clinical efficacy in the field of pediatrics. Patients treated were infants and children ranging from 2 months to 11 years old suffering from acute bronchitis in 5 cases, acute tonsillitis in 2 cases, Mycoplasma pneumonia in 2 cases, pertussis in 6 cases, scarlatina in 1 case and acute enteritis in 2 cases, a total of 18 cases. TE-031 was administered 19.7-43.5 mg/kg in daily doses and lengths of treatment ranged from 4 to 19 days. As regards to its clinical efficacy, good or excellent results were obtained in all cases: excellent in 11 cases and good in 7 cases. No clinical side effects nor abnormal laboratory test values obviously attributable to TE-031 were observed.

Jpn J Antibiot 1989 Apr;42(4):973-82

[Penetration of clarithromycin to saliva and its effect on normal salivary bacterial flora.]

[Article in Japanese]

Morihana T, Kaneko A, Tomita F, Suwa T, Kohno Y, Kobayashi I

Department of Oral Surgery, Ashikaga Red Cross Hospital.

Clarithromycin (TE-031, A-56268), a new macrolide antibiotic, was administered to rats, and the distribution of the drug in the submandibular gland was studied using microautoradiography. The study revealed good accumulation of 14C-TE-031 in both the acini and the excretory ducts. TE-031 was administered to each of 3 healthy male volunteers in a single dose of 300 mg, and its concentrations in the serum and saliva was detected. Mean values of various pharmacokinetic parameters were as follows for the serum and saliva, respectively. Cmax 1.49 micrograms/ml and 1.93 micrograms/ml; Tmax 2.91 hours and 2.66 hours; T 1/2 6.31 hours and 4.15 hours; AUC 18.58 micrograms.hr/ml and 17.70 micrograms.hr/ml. Regarding the salivary bacterial flora, the total bacterial count decreased as the salivary TE-031 concentration increased, but it recovered to the initial level in 12 hours after administration. During the 24-hour period following an administration of TE-031, the salivary bacteria did not acquire resistance to the drug. Therefore, TE-031 is an antibiotic which exerts little effect on the normal salivary bacterial flora in short-term administration. Although the results differed among the individuals, the penetration of TE-031 to saliva was superior to that to the serum. Thus, TDM of TE-031 using salivary samples is possible.

Curr Med Res Opin 1990;12(1):19-24

Comparative efficacy and tolerability of clarithromycin and amoxycillin in the treatment of out-patients with acute maxillary sinusitis.

Marchi E

Faculty of Medicine, University of Milan, Italy.

The efficacy and tolerability of clarithromycin and amoxycillin in the treatment of acute maxillary sinusitis were compared in an open, Phase III multi-centre study. Sixty-one out-patients (40 males, 21 females) received clarithromycin (two 250 mg tablets twice daily) and 59 (34 males, 25 females) out-patients received amoxycillin (two 500 mg capsules twice daily). Fifty-seven and 47 patients in the clarithromycin group were evaluable for clinical efficacy and bacteriological effectiveness, respectively. In the amoxycillin group, 57 and 40 patients were evaluated for clinical efficacy and bacteriological effectiveness, respectively. Body temperature, bacteriological culture results, blood and urine chemistries, and clinical signs and symptoms were evaluated prior to drug administration, between Days 4 to 6 and between Days 9 to 11 of treatment, and within 48 hours and, if required, 6 weeks after the end of treatment. Clinical signs and symptoms improved significantly (p less than 0.001) in both treatment groups. When evaluated within 48 hours after the end of treatment, there was no significant difference between the clinical success rate for clarithromycin (91%) and amoxycillin (84%) nor in the number of patients whose original pathogen was eradicated (89% clarithromycin, 93% amoxycillin). Six patients reported adverse events, 2 with clarithromycin (urticaria, gastro-intestinal) and 4 with amoxycillin (2 urticaria, 2 gastro-intestinal). Clarithromycin was comparable to amoxycillin with respect to clinical efficacy and tolerability and offers a useful addition to the available therapies for the treatment of acute maxillary sinusitis.

Curr Med Res Opin 1990;12(1):25-33

Comparison of the clinical and bacteriological efficacy of clarithromycin and erythromycin in the treatment of streptococcal pharyngitis.

Scaglione F

Faculty of Medicine, University of Milan, Italy.

The efficacy and tolerability of clarithromycin and erythromycin stearate in the treatment of documented Group A beta-haemolytic streptococcal pharyngitis were compared in a single-centre, open, out-patient study. One hundred and twenty patients were randomly assigned to each treatment group. Dosage of clarithromycin and erythromycin was 250 mg twice daily and 500 mg twice daily, respectively; each patient was given a 10-day supply of medication. Clinical success (cured or improved) was observed in 111 (96.5%) of 115 and in 108 (93.9%) of 115 clinically-evaluable patients treated with clarithromycin and erythromycin, respectively. Eradication of the pathogen occurred in 108 (97.3%) of 111 and in 98 (92.5%) of 106 bacteriologically-evaluable clarithromycin and erythromycin patients, respectively. Adverse events reported by 7 (5.8%) of the clarithromycin-treated and by 12 (10%) of the erythromycin-treated patients included epigastritis and nausea and vomiting. In general, the severity of adverse events was greater for the patients treated with erythromycin, necessitating the discontinuation of therapy in 8 (6.7%) patients treated with erythromycin as opposed to 1 (0.8%) patient treated with clarithromycin. Although clarithromycin and erythromycin were comparable in terms of efficacy, clarithromycin was better tolerated.

5.2 Pharmacokinetic properties:

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250-mg clarithromycin tablets was approximately 50%. Food slightly delays both the onset of clarithromycin absorption and the formation of the antimicrobially active metabolite, 14-OH clarithromycin, but does not affect the extent of bioavailability. Therefore, clarithromycin tablets may be given without regard to food.

In fasting healthy human subjects, peak serum concentrations were attained within 2 hours after oral dosing. Steady-state peak serum clarithromycin concentrations were attained in 2 to 3 days and were approximately 1 mcg/ml with a 250-mg dose administered every 12 hours, 2 to 3 mcg/ml with a 500 mg dose administered every 12 hours, and 3 to 4 mcg/ml with a 500-mg dose administered every 8 hours. The elimination half-life of clarithromycin was about 3 to 4 hours with 250 mg administered every 12 hours but increased to 5 to 7 hours with 500 mg administered every 8 to 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 8 to 12 hours. With a 250 mg every 12 hours dosing, the principal metabolite, 14-OH clarithromycin, attains a peak steady-state concentration of about 0.6 mcg/ml and has an elimination half-life of 5 to 6 hours. With a 500 mg every 8 to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is slightly higher (up to 1 mcg/ml), and its elimination half-life is about 7-9 hours. With any of these dosing regimens, the steady-state concentration of this metabolite is generally attained within 2 to 3 days.

After a 250-mg tablet every 12 hours, approximately 20% of the dose is excreted in the urine as clarithromycin, while after a 500-mg tablet every 12 hours, the urinary excretion of clarithromycin is somewhat greater, approximately 30%. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10% to 15% of the dose with either a 250-mg or a 500-mg tablet administered every 12 hours.

Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of 500-mg doses of clarithromycin every 12 hours to adult patients with HIV infection were similar to those observed in healthy volunteers. In adult HIV-infected patients taking 500- or 1000-mg doses of clarithromycin every 12 hours, steady-state clarithromycin C_{max} values ranged from 2 to 4 mcg/ml and 5 to 10 mcg/ml, respectively.

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 was also altered in subjects with impaired renal function.

Clarithromycin and the 14-OH clarithromycin metabolite distribute readily into body tissues and fluids. There are no data available on cerebrospinal fluid penetration. Because of high intracellular concentrations, tissue concentrations are higher than serum concentrations. Examples of tissue and serum concentrations are presented in the table below below.

Concentration (after 250 mg q12h)		
Tissue Type	**Tissue (µg/g)**	**Serum (µg/ml)**
Tonsil	1.6	0.8
Lung	8.8	1.7

J Antimicrob Chemother 2002 Nov;50(5):699-706

Pharmacokinetics of lansoprazole, amoxicillin and clarithromycin after simultaneous and single administration.

Mainz D, Borner K, Koeppe P, Kotwas J, Lode H

Department of Chest and Infectious Diseases, Hospital Heckeshorn-Zehlendorf, Berlin, Germany.

In a randomized, double-blind, placebo-controlled, four-way crossover study, possible influences of the triple therapy with amoxicillin, clarithromycin and the proton pump inhibitor lansoprazole on the pharmacokinetics of each of the drugs and the active 14-OH-clarithromycin metabolite were assessed. Twelve Helicobacter pylori-negative healthy male volunteers (age 27 +/- 4.3 years; creatinine clearance 7.0 +/- 2.0 L/h) were given lansoprazole 30 mg, amoxicillin 1 g and clarithromycin 500 mg, alone and in triple combination. Drug elimination intervals were at least 9 days between the dosing periods. The study medication was administered twice daily for 4 days. On the fifth day of each period, drugs were only given once in the morning, and blood and urine samples were collected for 12 h. The concentrations of the three substances administered, and 14-OH-clarithromycin, were determined by validated HPLC methods. Alterations in the serum kinetics were found for lansoprazole and the active 14-OH-clarithromycin metabolite (all data expressed as mean +/- S.D.). For lansoprazole, the elimination half-life (t(1/2)) was significantly prolonged (1.46 versus 1.7 h, $P < 0.05$) and the area under the concentration-time curve from 0 to 8 h (AUC(0-8)) was significantly increased (3.65 versus 4.59 mg.h/L, $P < 0.05$) by combination of the drugs. For 14-OH-clarithromycin, the peak concentration (C(max)) was 0.95 versus 1.18 mg/L and the AUC from 0 to 12 h (AUC(0-12)) was 8.3 versus 10.5 mg.h/L (augmented significantly, $P < 0.05$). The amoxicillin concentrations were slightly elevated by concomitant administration of lansoprazole and clarithromycin but without statistical significance (11.1 versus 12.6 mg/L). For clarithromycin, the time to maximum concentration of drug in serum (T(max)) was increased (2.73 versus 3.31 h, $P < 0.05$), whereas AUC and C(max) remained unchanged. Simultaneous administration of lansoprazole, amoxicillin and clarithromycin increases the serum concentrations of lansoprazole and the active 14-OH-clarithromycin metabolite significantly. These effects

were not so pronounced as to have any therapeutic influence, making dosage adjustment unnecessary.

Drug Metab Dispos 1990 Jul-Aug;18(4):441-6

Metabolism and disposition of clarithromycin in man.

Ferrero JL, Bopp BA, Marsh KC, Quigley SC, Johnson MJ, Anderson DJ, Lamm JE, Tolman KG, Sanders SW, Cavanaugh JH, et al

Drug Metabolism Department, Abbott Laboratories, Abbott Park, IL 60064-3500.

The metabolic fate and pharmacokinetics of clarithromycin following a single 250- or 1200-mg oral dose of 14C-clarithromycin were studied in six healthy adult males. Peak plasma levels of clarithromycin averaged 0.6 microgram/ml after the low dose and 2.7 micrograms/ml after the high dose. The AUC of clarithromycin increased 13-fold, with the 4.8-fold increase in dose, while the plasma half-life increased from 4.4 hr to 11.3 hr. The major metabolite in plasma and urine was the microbiologically active 14-hydroxylated-R epimer of clarithromycin. After 5 days, a mean of 38% of the low dose (18% as clarithromycin) and 46% of the high dose (29% as clarithromycin) was recovered in the urine, with approximately one-third eliminated during the first 24 hr. The nature of the urinary and fecal metabolites revealed the involvement of three metabolic pathways, viz. 1) hydroxylation at the 14-position to form the R and S epimers, 2) N-demethylation, and 3) hydrolysis of the cladinose sugar. Secondary metabolism via these pathways was also evident. The overall recovery of metabolites, but not total radioactivity, decreased 42% after the high dose. The nonlinear pharmacokinetic behavior of clarithromycin and the decrease in metabolite production suggest that clarithromycin metabolism can be saturated at high doses.

5.3 Preclinical safety data

The following in vitro mutagenicity tests have been conducted with clarithromycin:

- Salmonella/Mammalian Microsomes Test.
- Bacterial Induced Mutation Frequency Test.
- In Vitro Chromosome Aberration Test.
- Rat Hepatocyte DNA Synthesis Assay.
- Mouse Lymphoma Assay.
- Mouse Dominant Lethal Study.
- Mouse Micronucleus Test.

All tests had negative results except the In Vitro Chromosome Aberration Test which was 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.

Fertility and reproduction studies have shown that daily doses of up to 160 mg/kg/day (1.3 times the recommended maximum human dose based on mg/m2) 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 at 150 mg/kg/day (2.4 times the recommended maximum human dose based on mg/m2), 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/m2, which is 17 times less than the maximum proposed human oral daily dose of 618 mg/m2.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Lactose

Starch

Croscarmellose sodium

Microcrystalline cellulose

Methyl hydroxybenzoate

Magnesium stearate

Talc

Purified water

Hydroxy propyl methyl cellulose

Propylene glycol 6000

Propylene glycol

Titanium dioxide

Lake of Quinoline Yellow

Methylene chloride

Isopropyl alcohol

6.2 Incompatibilities

None of the In-active ingredients of the formulation have been known to exhibit incompatibility with the Active Ingredients.

6.3 Shelf-life

36 months.

6.4 Special precautions for storage

Store in a dry place below 25^{o}C. Protect from light.

6.5 Nature and contents of container

10 tablets are packed in one blister strip (PVDC coated PVC film / Aluminium foil). One blister strip along with one leaflet is packed in one inner carton. 10 such inner cartons are packed in an outer carton.

6.6 Instructions for use and handling

Store in a dry place below 25^{o}C. Protect from light.

Keep away from the reach of children.

7. MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

Shall be provided when available.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not Applicable.

10. DATE OF REVISION OF THE TEXT

Not Applicable.