# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 50-662 / S-028

# APPROVED LABELING

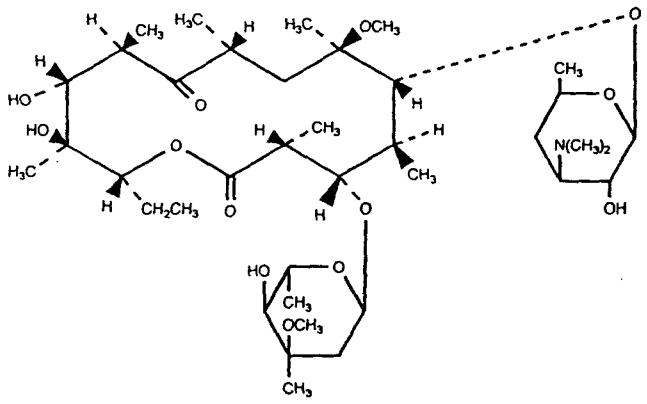
(Nos. 2586, 3163, 3188, 3368, 3494)
New

# BIAXIN® Filmtab®
(clarithromycin tablets)

# BIAXIN® Granules
(clarithromycin for oral suspension)

℞ ONLY

## DESCRIPTION
Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-*O*-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. The structural formula is:



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

BIAXIN is available as tablets and granules for oral suspension.

Each yellow oval film-coated BIAXIN tablet contains 250 mg or 500 mg of clarithromycin and the following inactive ingredients: cellulosic polymers, croscarmellose sodium, D&C Yellow No. 10, FD&C Blue No. 1, magnesium stearate, povidone, propylene glycol, silicon dioxide, sorbic acid, sorbitan monooleate, stearic acid, talc, titanium dioxide, and vanillin. The 250-mg tablet also contains pregelatinized starch.

After constitution, each 5 mL of BIAXIN suspension contains 125 mg, 187.5 mg or 250 mg of clarithromycin. Each bottle of BIAXIN granules contains 1250 mg (50-mL size), 2500 mg (50- and 100-mL sizes), 3750 mg (100-mL size), or 5000 mg (100-mL size) of clarithromycin and the following inactive ingredients: carbomer, castor oil, citric acid, hydroxypropyl methylcellulose phthalate, maltodextrin, potassium sorbate, povidone, silicon dioxide, sucrose, xanthan gum, titanium dioxide and fruit punch flavor.

## CLINICAL PHARMACOLOGY

**Pharmacokinetics:**

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, BIAXIN 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 $\mu$g/mL with a 250-mg dose administered every 12 hours, 2 to 3 $\mu$g/mL with a 500-mg dose administered every 12 hours, and 3 to 4 $\mu$g/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 $\mu$g/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 $\mu$g/mL), and its elimination half-life is about 7 to 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%. In comparison, after an oral dose of 250-mg (125 mg/5 mL) suspension every 12 hours, approximately 40% is excreted in urine as clarithromycin. 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 $\mu$g/mL and 5 to 10 $\mu$g/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. (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION.**)

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 below.

**CONCENTRATION**
(after 250 mg q 12 h)

| Tissue Type | Tissue ($\mu$g/g) | Serum ($\mu$g/mL) |
|---|---|---|
| Tonsil | 1.6 | 0.8 |
| Lung | 8.8 | 1.7 |

When 250-mg doses of clarithromycin as BIAXIN suspension were administered to fasting healthy adult subjects, peak plasma concentrations were attained around 3 hours after dosing. Steady-state peak plasma concentrations were attained in 2 to 3 days and were approximately 2 $\mu$g/mL for clarithromycin and 0.7 $\mu$g/mL for 14-OH clarithromycin when 250-mg doses of the clarithromycin suspension were administered every 12 hours. Elimination half-life of clarithromycin (3 to 4 hours) and that of 14-OH clarithromycin (5 to 7 hours) were similar to those observed at steady state following administration of equivalent doses of BIAXIN tablets.

For adult patients, the bioavailability of 10 mL of the 125-mg/5 mL suspension or 10 mL of the 250-mg/5 mL suspension is similar to a 250-mg or 500-mg tablet, respectively.

In children requiring antibiotic therapy, administration of 7.5 mg/kg q 12 h doses of clarithromycin as the suspension generally resulted in steady-state peak plasma concentrations of 3 to 7 $\mu$g/mL for clarithromycin and 1 to 2 $\mu$g/mL for 14-OH clarithromycin.

In HIV-infected children taking 15 mg/kg every 12 hours, steady-state clarithromycin peak concentrations generally ranged from 6 to 15 $\mu$g/mL.

Clarithromycin penetrates into the middle ear fluid of children with secretory otitis media.

**CONCENTRATION**
(after 7.5 mg/kg q 12 h for 5 doses)

| Analyte | Middle Ear Fluid ($\mu$g/mL) | Serum ($\mu$g/mL) |
|---|---|---|
| Clarithromycin | 2.5 | 1.7 |
| 14-OH Clarithromycin | 1.3 | 0.8 |

In adults given 250 mg clarithromycin as suspension (n=22), food appeared to decrease mean peak plasma clarithromycin concentrations from 1.2 (± 0.4) μg/mL to 1.0 (± 0.4) μg/mL and the extent of absorption from 7.2 (± 2.5) hr•μg/mL to 6.5 (± 3.7) hr•μg/mL.

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

Clarithromycin 500 mg every 8 hours was given in combination with omeprazole 40 mg daily to healthy adult males. The plasma levels of clarithromycin and 14-hydroxy-clarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean $C_{max}$ was 10% greater, the mean $C_{min}$ was 27% greater, and the mean $AUC_{0-8}$ was 15% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14-hydroxy-clarithromycin, the mean $C_{max}$ was 45% greater, the mean $C_{min}$ was 57% greater, and the mean $AUC_{0-8}$ was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

**Clarithromycin Tissue Concentrations 2 hours after Dose (μg/mL)/(μg/g)**

| Treatment | N | antrum | fundus | N | mucus |
|---|---|---|---|---|---|
| Clarithromycin | 5 | 10.48 ± 2.01 | 20.81 ± 7.64 | 4 | 4.15 ± 7.74 |
| Clarithromycin + Omeprazole | 5 | 19.96 ± 4.71 | 24.25 ± 6.37 | 4 | 39.29 ± 32.79 |

For information about other drugs indicated in combination with BIAXIN, refer to the CLINICAL PHARMACOLOGY section of their package inserts.

## Microbiology:

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 as described in the **INDICATIONS AND USAGE** section:

**Aerobic Gram-positive microorganisms**
*Staphylococcus aureus*
*Streptococcus pneumoniae*
*Streptococcus pyogenes*

**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.
**NOTE:** Most strains of methicillin-resistant and oxacillin-resistant staphylococci are resistant to clarithromycin.

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 as described in the **INDICATIONS AND USAGE** section.

**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 b.i.d. versus t.i.d. 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 $\mu$g/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 $\mu$g/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 $\mu$g/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 μg/mL. Two patients had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 μg/mL by E-test.

**Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes[a]**

| **Clarithromycin Pretreatment Results** | | **Clarithromycin Post-treatment Results** | | | |
|---|---|---|---|---|---|
| | | ***H. pylori* negative - eradicated** | ***H. pylori* positive - not eradicated Post-treatment susceptibility results** | | |
| | | | **S[b]** | **I[b]** | **R[b]** | **No MIC** |
| **Omeprazole 40 mg q.d./clarithromycin 500 mg t.i.d. for 14 days followed by omeprazole 20 mg q.d. for another 14 days (M93-067, M93-100)** | | | | | | |
| Susceptible[b] | 108 | 72 | 1 | | 26 | 9 |
| Intermediate[b] | 1 | | | | 1 | |
| Resistant[b] | 4 | | | | 4 | |
| **Ranitidine bismuth citrate 400 mg b.i.d./clarithromycin 500 mg t.i.d. for 14 days followed by ranitidine bismuth citrate 400 mg b.i.d. for another 14 days (H2BA3001)** | | | | | | |
| Susceptible[b] | 124 | 98 | 4 | | 14 | 8 |
| Intermediate[b] | 3 | 2 | | | | 1 |
| Resistant[b] | 17 | 1 | | | 15 | 1 |
| **Ranitidine bismuth citrate 400 mg b.i.d./clarithromycin 500 mg b.i.d. for 14 days followed by ranitidine bismuth citrate 400 mg b.i.d. for another 14 days (H2BA3001)** | | | | | | |
| Susceptible[b] | 125 | 106 | 1 | 1 | 12 | 5 |
| Intermediate[b] | 2 | 2 | | | | |
| Resistant[b] | 20 | 1 | | | 19 | |
| **Omeprazole 20 mg b.i.d./clarithromycin 500 mg b.i.d./amoxicillin 1 g b.i.d. for 10 days (126, 127, M96-446)** | | | | | | |
| Susceptible[b] | 171 | 153 | 7 | | 3 | 8 |
| Intermediate[b] | | | | | | |
| Resistant[b] | 14 | 4 | 1 | | 6 | 3 |

| | | | | |
|---|---|---|---|---|
| **Lansoprazole 30 mg b.i.d./clarithromycin 500 mg b.i.d./amoxicillin 1 g b.i.d. for 14 days (M95-399, M93-131, M95-392)** | | | | |
| Susceptible[b] | 112 | 105 | | 7 |
| Intermediate[b] | 3 | 3 | | |
| Resistant[b] | 17 | 6 | 7 | 4 |
| **Lansoprazole 30 mg b.i.d./clarithromycin 500 mg b.i.d./amoxicillin 1 g b.i.d. for 10 days (M95-399)** | | | | |
| Susceptible[b] | 42 | 40 | 1 | 1 |
| Intermediate[b] | | | | |
| Resistant[b] | 4 | 1 | 3 | |

[a] Includes only patients with pretreatment clarithromycin susceptibility tests

[b] 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 μg/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.

In the lansoprazole/clarithromycin amoxicillin triple-therapy clinical trials, 82.6% (195/236) of the patients that had pretreatment amoxicillin susceptible MICs (< 0.25 μg/mL) were eradicated of *H. pylori*. Of those with pretreatment amoxicillin MICs of > 0.25 μg/mL, three of six had the *H. pylori* eradicated. A total of 12.8% (22/172) of the patients failed the 10- and 14-day triple-therapy regimens. Post-treatment susceptibility results were not obtained on 11 of the patients who failed therapy. Nine of the 11 patients with amoxicillin post-treatment MICs that failed the triple-therapy regimen also had clarithromycin resistant *H. pylori* isolates.

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

**Aerobic Gram-positive microorganisms**
*Streptococcus agalactiae*
Streptococci (Groups C, F, G)
Viridans group streptococci

**Aerobic Gram-negative microorganisms**
*Bordetella pertussis*
*Legionella pneumophila*
*Pasteurella multocida*

**Anaerobic Gram-positive microorganisms**
*Clostridium perfringens*
*Peptococcus niger*
*Propionibacterium acnes*

**Anaerobic Gram-negative microorganisms**
*Prevotella melaninogenica* (formerly *Bacteriodes melaninogenicus*)

**Susceptibility Testing Excluding Mycobacteria and Helicobacter:**
*Dilution Techniques:*
Quantitative methods are used to determine antimicrobial 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 method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of clarithromycin powder. The MIC values should be interpreted according to the following criteria:

| MIC (µg/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. Standard clarithromycin powder should provide the following MIC values:

| Microorganism | MIC (µg/mL) |
|---|---|
| *S. aureus* ATCC 29213 | 0.12 to 0.5 |

*Diffusion Techniques:*
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] 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.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15-µg clarithromycin disk should be interpreted according to the following criteria:

| Zone diameter (mm) | Interpretation |
|---|---|
| ≥ 18 | Susceptible (S) |
| 14 to 17 | Intermediate (I) |
| ≤ 13 | Resistant (R) |

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for clarithromycin. However, standardized diffusion methods for routine *in vitro* susceptibility testing, using the 15-µg clarithromycin disk, do not measure the additive antimicrobial activity of the 14-OH metabolite and, thus, may underestimate the drug's potential activity against *Haemophilus influenzae*. *Haemophilus influenzae* isolates falling into the "Intermediate" category often respond to treatment.

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-µg clarithromycin disk should provide the following zone diameters in this laboratory test quality control strain:

| Microorganism | Zone diameter (mm) |
|---|---|
| *S. aureus* ATCC 25923 | 26 to 32 |

***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 $\leq$ 4.0 $\mu$g/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 $\leq$ 0.5 $\mu$g/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 $\mu$g/mL. Clarithromycin inhibited all isolates at > 10.0 $\mu$g/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 ($1 \times 10^7$ - $1 \times 10^8$ 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 following criteria:

| Clarithromycin MIC ($\mu$g/mL)[a] | Interpretation |
|---|---|
| < 0.25 | Susceptible (S) |
| 0.5 - 1.0 | Intermediate (I) |
| > 2.0 | Resistant (R) |
| **Amoxicillin MIC ($\mu$g/mL)[a,b]** | **Interpretation** |
| < 0.25 | Susceptible (S) |

[a] These are tentative breakpoints for the agar dilution methodology, and they should not be used to interpret results obtained using alternative methods.

[b] There were not enough organisms with MICs > 0.25 $\mu$g/mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

| Microorganisms | Antimicrobial Agent | MIC ($\mu$g/mL)[c] |
|---|---|---|
| *H. pylori* ATCC 43504 | Clarithromycin | 0.015 - 0.12 $\mu$g/mL |
| *H. pylori* ATCC 43504 | Amoxicillin | 0.015 - 0.12 $\mu$g/mL |

[c] These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

## INDICATIONS AND USAGE

BIAXIN Filmtab tablets and BIAXIN Granules for oral suspension are indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

**Adults:**

Pharyngitis/Tonsillitis due to *Streptococcus pyogenes* (The usual drug of choice in the treatment and prevention of streptococcal infections and the prophylaxis of rheumatic fever is penicillin administered by either the intramuscular 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 available at present.)

Acute maxillary sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*

Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*

Pneumonia due to *Mycoplasma pneumoniae*, *Streptococcus pneumoniae,* or *Chlamydia pneumoniae* (TWAR)

Uncomplicated skin and skin structure infections due to *Staphylococcus aureus*, or *Streptococcus pyogenes* (Abscesses usually require surgical drainage.)

Disseminated mycobacterial infections due to *Mycobacterium avium*, or *Mycobacterium intracellulare*

BIAXIN (clarithromycin) Filmtab tablets in combination with amoxicillin and PREVACID (lansoprazole) or PRILOSEC (omeprazole) Delayed-Release Capsules, as triple therapy, are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or five-year history of duodenal ulcer) to eradicate *H. pylori*.

BIAXIN Filmtab tablets in combination with PRILOSEC (omeprazole) capsules or TRITEC (ranitidine bismuth citrate) tablets are also indicated for the treatment of patients with an active duodenal ulcer associated with *H. pylori* infection. However, regimens which contain clarithromycin as the single antimicrobial agent are more likely to be associated with the development of clarithromycin resistance among patients who fail therapy. Clarithromycin-containing regimens should not be used in patients with known or suspected clarithromycin resistant isolates because the efficacy of treatment is reduced in this setting.

In patients who fail therapy, susceptibility testing should be done if possible. If resistance to clarithromycin is demonstrated, a non-clarithromycin-containing therapy is recommended. (For information on development of resistance see **Microbiology** section.) The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence.

**Children:**
Pharyngitis/Tonsillitis due to *Streptococcus pyogenes*

Pneumonia due to *Mycoplasma pneumoniae*, *Streptococcus pneumoniae,* or *Chlamydia pneumoniae* (TWAR)

Acute maxillary sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*

Acute otitis media due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*

**NOTE:** For information on otitis media, see **CLINICAL STUDIES: Otitis Media.**

Uncomplicated skin and skin structure infections due to *Staphylococcus aureus*, or *Streptococcus pyogenes* (Abscesses usually require surgical drainage.)

Disseminated mycobacterial infections due to *Mycobacterium avium*, or *Mycobacterium intracellulare*

**Prophylaxis:**
BIAXIN Filmtab tablets and BIAXIN Granules for oral suspension are indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection.

## CONTRAINDICATIONS

Clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, or any of the macrolide antibiotics.

Concomitant administration of clarithromycin with cisapride, pimozide, or terfenadine is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, pimozide, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of hepatic metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

For information about contraindications of other drugs indicated in combination with BIAXIN, refer to the CONTRAINDICATIONS section of their package inserts.

## 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. (See PRECAUTIONS - *Pregnancy*.)**

**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.

For information about warnings of other drugs indicated in combination with BIAXIN, refer to the WARNINGS section of their package inserts.

## 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. (See **DOSAGE AND ADMINISTRATION.**)

Clarithromycin in combination with ranitidine bismuth citrate should not be used in patients with a history of acute porphyria.

For information about precautions of other drugs indicated in combination with BIAXIN, refer to the PRECAUTIONS section of their package inserts.

*Information to Patients*: BIAXIN tablets and oral suspension can be taken with or without food and can be taken with milk. Do **NOT** refrigerate the suspension.

*Drug Interactions:* 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 $C_{max}$, $C_{min}$, 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. (See **CONTRAINDICATIONS.**)

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 ($C_{max}$, $AUC_{0-24}$, and $T_{1/2}$ 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 BIAXIN tablets 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 BIAXIN tablets were administered two to four hours prior to oral zidovudine, the steady-state zidovudine $C_{max}$ was increased by approximately 2-fold, whereas the AUC was unaffected.

Simultaneous administration of BIAXIN tablets 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 $C_{min}$ and AUC of 33% and 18%, respectively. Steady-state concentrations of 14-OH clarithromycin were not significantly affected by concomitant administration of fluconazole.

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 $CL_{CR}$ 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%.

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.

*Carcinogenesis, Mutagenesis, Impairment of Fertility:*
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 $mg/m^2$) 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 $mg/m^2$), clarithromycin was shown to produce embryonic loss in monkeys. This effect has been attributed to marked maternal toxicity of the drug at this high dose.

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

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

*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 $mg/m^2$) 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 $mg/m^2$, 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 $mg/m^2$) 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. (See **WARNINGS**.)

*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.

*Pediatric Use:* Safety and effectiveness of clarithromycin in pediatric patients under 6 months of age have not been established. 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.

*Geriatric Use:* 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 serum concentrations and area under the curves of clarithromycin and 14-OH clarithromycin were increased compared to those achieved in healthy young adults. 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. Dosage adjustment should be considered in elderly patients with severe renal impairment.

## ADVERSE REACTIONS

The majority of side effects observed in clinical trials were of a mild and transient nature. Fewer than 3% of adult patients without mycobacterial infections and fewer than 2% of pediatric patients without mycobacterial infections discontinued therapy because of drug-related side effects.

The most frequently reported events in adults were diarrhea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). In pediatric patients, the most frequently reported events were diarrhea (6%), vomiting (6%), abdominal pain (3%), rash (3%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% was described as severe.

In pneumonia studies conducted in adults comparing clarithromycin to erythromycin base or erythromycin stearate, there were fewer adverse events involving the digestive system in clarithromycin-treated patients compared to erythromycin-treated patients (13% vs 32%; $p<0.01$). Twenty percent of erythromycin-treated patients discontinued therapy due to adverse events compared to 4% of clarithromycin-treated patients.

In two U.S. studies of acute otitis media comparing clarithromycin to amoxicillin/potassium clavulanate in pediatric patients, there were fewer adverse events involving the digestive system in clarithromycin-treated patients compared to amoxicillin/potassium clavulanate-treated patients (21% vs. 40%, $p<0.001$). One-third as many clarithromycin-treated patients reported diarrhea as did amoxicillin/potassium clavulanate-treated patients.

*Post-Marketing Experience:*

Allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis, ~~and~~ Stevens-Johnson syndrome, and ~~toxic epidermal necrolysis~~ have occurred. Other spontaneously reported adverse events include glossitis, stomatitis, oral moniliasis, ~~anorexia~~, vomiting, tongue discoloration, thrombocytopenia, leukopenia, neutropenia, and dizziness. There have been reports of tooth discoloration in patients treated with BIAXIN. Tooth discoloration is usually reversible with professional dental cleaning. There have been isolated reports of hearing loss, which is usually reversible, occurring chiefly in elderly women. Reports of alterations of the sense of smell, usually in conjunction with taste perversion or taste loss have also been reported.

Transient CNS events including anxiety, behavioral changes, confusional states, depersonalization, disorientation, hallucinations, insomnia, manic behavior, nightmares, psychosis, tinnitus, tremor, and vertigo have been reported during post-marketing surveillance. Events usually resolve with discontinuation of the drug.

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

There have been rare reports of hypoglycemia, some of which have occurred in patients taking oral hypoglycemic agents or insulin.

As with other macrolides, clarithromycin has been associated with QT prolongation and

ventricular arrhythmias, including ventricular tachycardia and torsades de pointes.
*Changes in Laboratory Values:* Changes in laboratory values with possible clinical significance were as follows:

Hepatic - elevated SGPT (ALT) < 1%; SGOT (AST) < 1%; GGT < 1%; alkaline phosphatase <1%; LDH < 1%; total bilirubin < 1%

Hematologic - decreased WBC < 1%; elevated prothrombin time 1%

Renal - elevated BUN 4%; elevated serum creatinine < 1%

GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.

## DOSAGE AND ADMINISTRATION

BIAXIN® Filmtab® (clarithromycin tablets) and BIAXIN® Granules (clarithromycin for oral suspension) may be given with or without food.

**ADULT DOSAGE GUIDELINES**

| 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
Triple therapy: BIAXIN/lansoprazole/amoxicillin
The recommended adult dose is 500 mg BIAXIN, 30 mg lansoprazole, and 1 gram amoxicillin, all given twice daily (q12h) for 10 or 14 days. (See **INDICATIONS AND USAGE** and **CLINICAL STUDIES** sections.)

Triple therapy: BIAXIN/omeprazole/amoxicillin
The recommended adult dose is 500 mg BIAXIN, 20 mg omeprazole, and 1 gram amoxicillin, all given twice daily (q12h) for 10 days. (See **INDICATIONS AND USAGE** and **CLINICAL**

**STUDIES** sections.) In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.

Dual therapy: BIAXIN/omeprazole
The recommended adult dose is 500 mg BIAXIN given three times daily (q8h) and 40 mg omeprazole given once daily (qAM) for 14 days. (See **INDICATIONS AND USAGE** and **CLINICAL STUDIES** sections.) An additional 14 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.

Dual therapy: BIAXIN/ranitidine bismuth citrate
The recommended adult dose is 500 mg BIAXIN given twice daily (q12h) or three times daily (q8h) and 400 mg ranitidine bismuth citrate given twice daily (q12h) for 14 days. An additional 14 days of 400 mg twice daily is recommended for ulcer healing and symptom relief. BIAXIN and ranitidine bismuth citrate combination therapy is not recommended in patients with creatinine clearance less than 25 mL/min. (See **INDICATIONS AND USAGE** and **CLINICAL STUDIES** sections.)

Children - The usual recommended daily dosage is 15 mg/kg/day divided q12h for 10 days.

**PEDIATRIC DOSAGE GUIDELINES**

**Based on Body Weight**

**Dosing Calculated on 7.5 mg/kg q12h**

| Weight | | Dose | | | |
|---|---|---|---|---|---|
| **Kg** | **lbs** | **(q12h)** | **125 mg/5 mL** | **187.5 mg/mL** | **250 mg/5 mL** |
| 9 | 20 | 62.5 mg | 2.5 mL q12h | 1.67 mL q12h | 1.25 mL q12h |
| 17 | 37 | 125 mg | 5.0 mL q12h | 3.33 mL q12h | 2.5 mL q12h |
| 25 | 55 | 187.5 mg | 7.5 mL q12h | 5.0 mL q12h | 3.75 mL q12h |
| 33 | 73 | 250 mg | 10 mL q12h | 6.67 mL q12h | 5.0 mL q12h |

Clarithromycin may be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function. However, in the presence of severe renal impairment ($CR_{CL}$ < 30 mL/min), with or without coexisting hepatic impairment, the dose should be halved or the dosing interval doubled.

*Mycobacterial infections:*
*Prophylaxis:* The recommended dose of BIAXIN for the prevention of disseminated *Mycobacterium avium* disease is 500 mg b.i.d. In children, the recommended dose is 7.5 mg/kg b.i.d. up to 500 mg b.i.d. No studies of clarithromycin for MAC prophylaxis have been performed in pediatric populations and the doses recommended for prophylaxis are derived from

MAC treatment studies in children. Dosing recommendations for children are in the table above.

*Treatment:* Clarithromycin is recommended as the primary agent for the treatment of disseminated infection due to *Mycobacterium avium* complex. Clarithromycin should be used in combination with other antimycobacterial drugs that have shown *in vitro* activity against MAC or clinical benefit in MAC treatment. (See **CLINICAL STUDIES.**) The recommended dose for mycobacterial infections in adults is 500 mg b.i.d. In children, the recommended dose is 7.5 mg/kg b.i.d. up to 500 mg b.i.d. Dosing recommendations for children are in the table above.

Clarithromycin therapy should continue for life if clinical and mycobacterial improvements are observed.

**Constituting Instructions**

The table below indicates the volume of water to be added when constituting:

| Total volume after constitution | Clarithromycin concentration after constitution | Amount of water to be added* |
|---|---|---|
| 50 mL | 125 mg/5 mL | 27 mL |
| 100 mL | 125 mg/5 mL | 55 mL |
| 100 mL | 187.5 mg/5 mL | 55 mL |
| 50 mL | 250 mg/5 mL | 27 mL |
| 100 mL | 250 mg/5 mL | 55 mL |

* see instructions below.

Add half the volume of water to the bottle and shake vigorously. Add the remainder of water to the bottle and shake.

Shake well before each use. Oversize bottle provides shake space. Keep tightly closed. Do not refrigerate. After mixing, store at 15° to 30°C (59° to 86°F) and use within 14 days.

## HOW SUPPLIED

BIAXIN® Filmtab® (clarithromycin tablets) are supplied as yellow oval film-coated tablets imprinted (on one side) in blue with the Abbott logo and a two-letter Abbo-Code designation, KT for the 250-mg tablet and KL for the 500-mg tablet, in the following packaging sizes:
250-mg tablets:
Bottles of 60 (**NDC** 0074-3368-60) and ABBO-PAC unit dose strip packages of 100 (**NDC** 0074-3368-11).
500-mg tablets:
Bottles of 60 (**NDC** 0074-2586-60), ABBO-PAC unit dose strip packages of 100 (**NDC** 0074-2586-11), BIAXIN 7-PAK® unit-of-use package of 14 tablets in individual blisters (**NDC** 0074-2586-41).

BIAXIN® Granules (clarithromycin for oral suspension) is supplied in the following strengths and sizes:

| Total volume after constitution | Clarithromycin concentration after constitution | Clarithromycin contents per bottle | NDC |
|---|---|---|---|
| 50 mL | 125 mg/5 mL | 1250 mg | 0074-3163-50 |
| 100 mL | 125 mg/5 mL | 2500 mg | 0074-3163-13 |
| 100 mL | 187.5 mg/5 mL | 3750 mg | 0074-3494-13 |
| 50 mL | 250 mg/5 mL | 2500 mg | 0074-3188-50 |
| 100 mL | 250 mg/5 mL | 5000 mg | 0074-3188-13 |

Store tablets and granules for oral suspension at controlled room temperature 15° to 30°C (59° to 86°F) in a well-closed container. Protect from light. Do not refrigerate BIAXIN suspension.

## CLINICAL STUDIES

### Mycobacterial Infections

**Prophylaxis:**

A randomized, double-blind study (561) compared clarithromycin 500 mg b.i.d. to placebo in patients with CDC-defined AIDS and $CD_4$ counts < 100 cells/μL. This study accrued 682 patients from November 1992 to January 1994, with a median $CD_4$ cell count at study entry of 30 cells/μL. Median duration of clarithromycin was 10.6 months vs. 8.2 months for placebo. 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 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. The study was designed to evaluate the following endpoints:

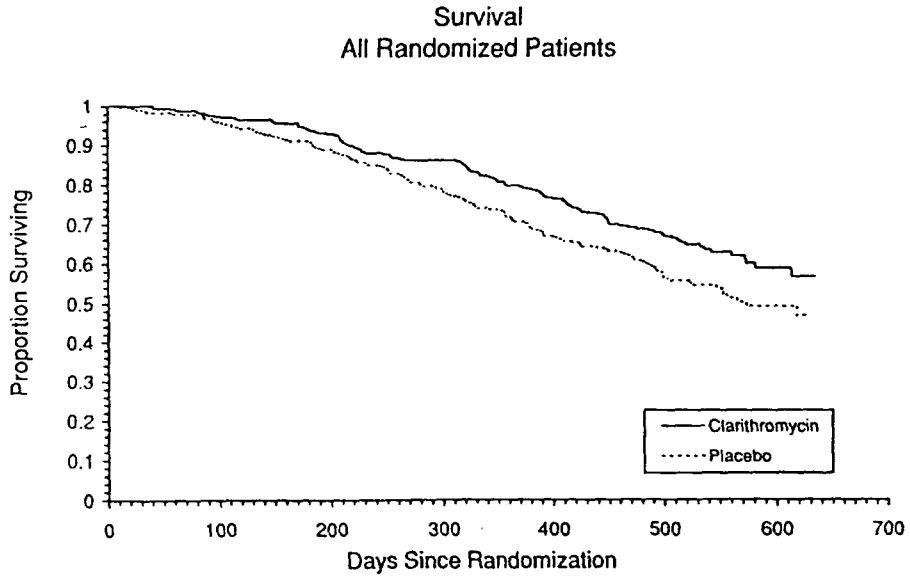
1. MAC bacteremia, defined as at least one positive culture for *M. avium* complex bacteria from blood or another normally sterile site.
2. Survival.
3. Clinically significant disseminated MAC disease, defined as MAC bacteremia accompanied by signs or symptoms of serious MAC infection, including fever, night sweats, weight loss, anemia, or elevations in liver function tests.

*MAC bacteremia:*

In patients randomized to clarithromycin, the risk of MAC bacteremia was reduced by 69% compared to placebo. The difference between groups was statistically significant ($p<0.001$). 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. 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$^3$ (range 2 to 130 cells/mm$^3$) for placebo patients that developed MAC.

*Survival:*
A statistically significant survival benefit was observed.




| | Mortality | | Reduction in |
|---|---|---|---|
| | **Placebo** | **Clarithromycin** | **Mortality on Clarithromycin** |
| 6 month | 9.4% | 6.5% | 31% |
| 12 month | 29.7% | 20.5% | 31% |
| 18 month | 46.4% | 37.5% | 20% |

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

*Clinically significant disseminated MAC disease:*
In association with the decreased incidence of bacteremia, patients in the group randomized to clarithromycin showed reductions in the signs and symptoms of disseminated MAC disease, including fever, night sweats, weight loss, and anemia.

*Safety:*
In AIDS patients treated with clarithromycin over long periods of time for prophylaxis against *M. avium*, it was often difficult to distinguish adverse events possibly associated with

clarithromycin administration from underlying HIV disease or intercurrent illness. Median duration of treatment was 10.6 months for the clarithromycin group and 8.2 months for the placebo group.

Treatment-related* Adverse Event Incidence Rates (%) in Immunocompromised Adult Patients Receiving Prophylaxis Against *M. avium* Complex

| Body System‡<br>Adverse Event | Clarithromycin<br>(n = 339)<br>% | Placebo<br>(n = 339)<br>% |
|---|---|---|
| Body as a Whole | | |
| Abdominal pain | 5.0% | 3.5% |
| Headache | 2.7% | 0.9% |
| Digestive | | |
| Diarrhea | 7.7% | 4.1% |
| Dyspepsia | 3.8% | 2.7% |
| Flatulence | 2.4% | 0.9% |
| Nausea | 11.2% | 7.1% |
| Vomiting | 5.9% | 3.2% |
| Skin & Appendages | | |
| Rash | 3.2% | 3.5% |
| Special Senses | | |
| Taste Perversion | 8.0% | 0.3% |

* Includes those events possibly or probably related to study drug and excludes concurrent conditions.

‡ > 2% Adverse Event Incidence Rates for either treatment group.

Among these events, taste perversion was the only event that had significantly higher incidence in the clarithromycin-treated group compared to the placebo-treated group.

Discontinuation due to adverse events was required in 18% of patients receiving clarithromycin compared to 17% of patients receiving placebo in this trial. Primary reasons for discontinuation in clarithromycin treated patients include headache, nausea, vomiting, depression and taste perversion.

*Changes in Laboratory Values of Potential Clinical Importance:*
In immunocompromised patients receiving prophylaxis against *M. avium*, evaluations of laboratory values were made by analyzing those values outside the seriously abnormal value (i.e., the extreme high or low limit) for the specified test.

**Percentage of Patients[a] Exceeding Extreme Laboratory Value in Patients Receiving Prophylaxis Against *M. avium* Complex**

| | | Clarithromycin 500 mg b.i.d. | | Placebo | |
|---|---|---|---|---|---|
| Hemoglobin | < 8 g/dL | 4/118 | 3% | 5/103 | 5% |
| Platelet Count | < 50 x $10^9$/L | 11/249 | 4% | 12/250 | 5% |
| WBC Count | < 1 x $10^9$/L | 2/103 | 4% | 0/95 | 0% |
| SGOT | > 5 x ULN[b] | 7/196 | 4% | 5/208 | 2% |
| SGPT | > 5 x ULN[b] | 6/217 | 3% | 4/232 | 2% |
| Alk. Phos. | > 5 x ULN[b] | 5/220 | 2% | 5/218 | 2% |

[a] 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).

[b] ULN = Upper Limit of Normal

**Treatment:**

Three randomized studies (500, 577, and 521) compared different dosages of clarithromycin in patients with CDC-defined AIDS and $CD_4$ counts <100 cells/$\mu$L. These studies accrued patients from May 1991 to March 1992. Study 500 was randomized, double-blind; Study 577 was open-label compassionate use. Both studies used 500 and 1000 mg b.i.d. doses; Study 500 also had a 2000 mg b.i.d. group. Study 521 was a pediatric study at 3.75, 7.5, and 15 mg/kg b.i.d. Study 500 enrolled 154 adult patients, Study 577 enrolled 469 adult patients, and Study 521 enrolled 25 patients between the ages of 1 to 20. The majority of patients had $CD_4$ cell counts <50/$\mu$L at study entry. The studies were designed to evaluate the following end points:

1. Change in MAC bacteremia or blood cultures negative for *M. avium*.
2. 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.

The results for the 500 study are described below. The 577 study results were similar to the results of the 500 study. Results with the 7.5 mg/kg b.i.d. dose in the pediatric study were comparable to those for the 500 mg b.i.d. regimen in the adult studies.

Study 069 compared the safety and efficacy of clarithromycin in combination with ethambutol versus clarithromycin in combination with ethambutol and clofazimine for the treatment of disseminated MAC (dMAC) infection[4]. This 24-week study enrolled 106 patients with AIDS and dMAC, with 55 patients randomized to receive clarithromycin and ethambutol, and 51 patients randomized to receive clarithromycin, ethambutol, and clofazimine. Baseline characteristics between study arms were similar with the exception of median CFU counts being at least 1 log higher in the clarithromycin, ethambutol, and clofazimine arm.

Compared to prior experience with clarithromycin monotherapy, the two drug regimen of clarithromycin and ethambutol was well tolerated and extended the time to microbiologic relapse, largely through suppressing the emergence of clarithromycin resistant strains. However,

the addition of clofazamine to the regimen added no additional microbiologic or clinical benefit. Tolerability of both multidrug regimens was comparable with the most common adverse events being gastrointestinal in nature. Patients receiving the clofazimine-containing regimen had reduced survival rates; however, their baseline mycobacterial colony counts were higher. The results of this trial support the addition of ethambutol to clarithromycin for the treatment of initial dMAC infections but do not support adding clofazimine as a third agent.

*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[5] (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.

**Mean Reductions in Log CFU from Baseline (After 4 Weeks of Therapy)**

| 500 mg b.i.d. (N=35) | 1000 mg b.i.d. (N=32) | 2000 mg b.i.d. (N=26) | Four Drug Regimen (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 of 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% (25/48) 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 an MIC < 8 $\mu$g/mL at pre-treatment. 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. The time to first decrease of at least 1 log in CFU count was significantly shorter with the 1000 and 2000 mg b.i.d. doses (median equal to 16 and 15 days, respectively) in comparison to the 500 mg b.i.d. group (median equal to 29 days). The median time to first positive culture or study discontinuation following the first negative culture was 43, 59 and 43 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 below:

| **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 gm** | | |
|---|---|---|---|---|---|
| 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 or 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.[5]

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.

*Safety:*
The adverse event profiles showed that both the 500 and 1000 mg b.i.d. doses were well tolerated. The 2000 mg b.i.d. dose was poorly tolerated and resulted in a higher proportion of premature discontinuations.

In AIDS patients and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of HIV disease or intercurrent illness.

The following analyses summarize experience during the first 12 weeks of therapy with clarithromycin. Data are reported separately for Study 500 (randomized, double-blind) and Study 577 (open-label, compassionate use) and also combined. Adverse events were reported less frequently in Study 577, which may be due in part to differences in monitoring between the two studies. In adult patients receiving clarithromycin 500 mg b.i.d., the most frequently reported adverse events, considered possibly or probably related to study drug, with an incidence of 5% or greater, are listed below. Most of these events were mild to moderate in severity, although 5% (Study 500: 8%; Study 577: 4%) of patients receiving 500 mg b.i.d. and 5% (Study 500: 4%; Study 577: 6%) of patients receiving 1000 mg b.i.d. reported severe adverse events. Excluding those patients who discontinued therapy or died due to complications of their underlying non-mycobacterial disease, approximately 8% (Study 500: 15%; Study 577: 7%) of the patients who received 500 mg b.i.d. and 12% (Study 500: 14%; Study 577: 12%) of the patients who received 1000 mg b.i.d. discontinued therapy due to drug-related events during the first 12 weeks of therapy. Overall, the 500 and 1000 mg b.i.d. doses had similar adverse event profiles.

**Treatment-related* Adverse Event Incidence Rates (%) in Immunocompromised Adult Patients During the First 12 Weeks of Therapy with 500 mg b.i.d. Clarithromycin Dose**

| Adverse Event | Study 500 (n=53) | Study 577 (n=255) | Combined (n=308) |
|---|---|---|---|
| Abdominal Pain | 7.5 | 2.4 | 3.2 |
| Diarrhea | 9.4 | 1.6 | 2.9 |
| Flatulence | 7.5 | 0.0 | 1.3 |
| Headache | 7.5 | 0.4 | 1.6 |
| Nausea | 28.3 | 9.0 | 12.3 |
| Rash | 9.4 | 2.0 | 3.2 |
| Taste Perversion | 18.9 | 0.4 | 3.6 |
| Vomiting | 24.5 | 3.9 | 7.5 |

* Includes those events possibly or probably related to study drug and excludes concurrent conditions.

A limited number of pediatric AIDS patients have been treated with clarithromycin suspension for mycobacterial infections. The most frequently reported adverse events, excluding those due to the patient's concurrent condition, were consistent with those observed in adult patients.

*Changes in Laboratory Values:*
In immunocompromised patients treated with clarithromycin for mycobacterial infections, evaluations of laboratory values were made by analyzing those values outside the seriously abnormal level (i.e., the extreme high or low limit) for the specified test.

**Percentage of Patients[a] Exceeding Extreme Laboratory Value Limits During First 12 Weeks of Treatment 500 mg b.i.d. Dose[b]**

| | | Study 500 | Study 577 | Combined |
|---|---|---|---|---|
| BUN | >50 mg/dL | 0% | <1% | <1% |
| Platelet Count | <50 x $10^9$/L | 0% | <1% | <1% |
| SGOT | >5 x ULN[c] | 0% | 3% | 2% |
| SGPT | >5 x ULN[c] | 0% | 2% | 1% |
| WBC | <1 x $10^9$/L | 0% | 1% | 1% |

[a] 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)
[b] Includes all values within the first 12 weeks for patients who start on 500 mg b.i.d.
[c] ULN = Upper Limit of Normal

## Otitis Media

In a controlled clinical study of acute otitis media performed in the United States, where significant rates of beta-lactamase producing organisms were found, clarithromycin was compared to an oral cephalosporin. In this study, very strict evaluability criteria were used to determine clinical response. For the 223 patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the post-therapy visit was 88% for clarithromycin and 91% for the cephalosporin.

In a smaller number of patients, microbiologic determinations were made at the pre-treatment visit. The following presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) were obtained:

**U.S. Acute Otitis Media Study**
**Clarithromycin vs. Oral Cephalosporin**

**EFFICACY RESULTS**

| PATHOGEN | OUTCOME |
|---|---|
| *S. pneumoniae* | clarithromycin success rate, 13/15 (87%), control 4/5 |
| *H. influenzae** | clarithromycin success rate, 10/14 (71%), control 3/4 |
| *M. catarrhalis* | clarithromycin success rate, 4/5, control 1/1 |
| *S. pyogenes* | clarithromycin success rate, 3/3, control 0/1 |
| Overall | clarithromycin success rate 30/37 (81%), control 8/11 (73%) |

* None of the *H. influenzae* isolated pre-treatment was resistant to clarithromycin; 6% were resistant to the control agent.

*Safety:*
The incidence of adverse events in all patients treated, primarily diarrhea and vomiting, did not differ clinically or statistically for the two agents.

In two other controlled clinical trials of acute otitis media performed in the United States, where significant rates of beta-lactamase producing organisms were found, clarithromycin was compared to an oral antimicrobial agent that contained a specific beta-lactamase inhibitor. In these studies, very strict evaluability criteria were used to determine the clinical responses. In the 233 patients who were evaluated for clinical efficacy, the combined clinical success rate (i.e., cure and improvement) at the post-therapy visit was 91% for both clarithromycin and the control.

For the patients who had microbiologic determinations at the pre-treatment visit, the following presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) were obtained:

**Two U.S. Acute Otitis Media Studies Clarithromycin vs. Antimicrobial/Beta-lactamase Inhibitor**

**EFFICACY RESULTS**

| PATHOGEN | OUTCOME |
|---|---|
| *S. pneumoniae* | clarithromycin success rate, 43/51 (84%), control 55/56 (98%) |
| *H. influenzae** | clarithromycin success rate, 36/45 (80%), control 31/33 (94%) |
| *M. catarrhalis* | clarithromycin success rate, 9/10 (90%), control 6/6 |
| *S. pyogenes* | clarithromycin success rate, 3/3, control 5/5 |
| Overall | clarithromycin success rate, 91/109 (83%), control 97/100 (97%) |

* Of the *H. influenzae* isolated pre-treatment, 3% were resistant to clarithromycin and 10% were resistant to the control agent.

*Safety:*
The incidence of adverse events in all patients treated, primarily diarrhea (15% vs. 38%) and diaper rash (3% vs. 11%) in young children, was clinically and statistically lower in the clarithromycin arm versus the control arm.

**Duodenal Ulcer Associated with *H. pylori* Infection**
**Clarithromycin + Lansoprazole and Amoxicillin**
*H. pylori Eradication for Reducing the Risk of Duodenal Ulcer Recurrence:*
Two U.S. randomized, double-blind clinical studies in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an active ulcer within one year) evaluated the efficacy of clarithromycin in combination with lansoprazole and amoxicillin capsules as triple 14-day therapy for eradication of *H. pylori*. Based on the results of these studies, the safety and efficacy of the following eradication regimen were established:

Triple therapy: BIAXIN 500 mg b.i.d. + lansoprazole 30 mg b.i.d. + amoxicillin 1 gm b.i.d.

Treatment was for 14 days. *H. pylori* eradication was defined as two negative tests (culture and histology) at 4 to 6 weeks following the end of treatment.

The combination of BIAXIN plus lansoprazole and amoxicillin as triple therapy was effective in eradicating *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

A randomized, double-blind clinical study performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) compared the efficacy of clarithromycin in combination with lansoprazole and amoxicillin as triple therapy for 10 and 14 days. This study established that the 10-day triple therapy was equivalent to the 14-day triple therapy in eradicating *H. pylori*.

***H. pylori* Eradication Rates-Triple Therapy (BIAXIN/lansoprazole/amoxicillin)**
**Percent of Patients Cured [95% Confidence Interval]**
**(number of patients)**

| Study | Duration | Triple Therapy Evaluable Analysis* | Triple Therapy Intent-to-Treat Analysis# |
|---|---|---|---|
| M93-131 | 14 days | 92† [80.0 - 97.7] (n = 48) | 86† [73.3 - 93.5] (n=55) |
| M95-392 | 14 days | 86‡ [75.7 - 93.6] (n = 66) | 83‡ [72.0 - 90.8] (n = 70) |
| M95-399¶ | 14 days | 85 [77.0 - 91.0] (N = 113) | 82 [73.9 - 88.1] (N = 126) |
| | 10 days | 84 [76.0 - 89.8] (N = 123) | 81 [73.9 - 87.6] (N = 135) |

* Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest (Delta West LTD., Bentley, Australia), histology, and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients were dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as evaluable failures of therapy.

\# Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of therapy.

† ($p<0.05$) versus BIAXIN/lansoprazole and lansoprazole/amoxicillin dual therapy.

‡ ($p<0.05$) versus BIAXIN/amoxicillin dual therapy.

¶ The 95% confidence interval for the difference in eradication rates, 10-day minus 14-day, is (-10.5, 8.1) in the evaluable analysis and (-9.7, 9.1) in the intent-to-treat analysis.

## Clarithromycin + Omeprazole and Amoxicillin Therapy

*H. pylori Eradication for Reducing the Risk of Duodenal Ulcer Recurrence:*

Three U.S., randomized, double-blind clinical studies in patients with *H. pylori* infection and duodenal ulcer disease (n = 558) compared clarithromycin plus omeprazole and amoxicillin to clarithromycin plus amoxicillin. Two studies (Studies 126 and 127) were conducted in patients with an active duodenal ulcer, and the third study (Study 446) was conducted in patients with a duodenal ulcer in the past 5 years, but without an ulcer present at the time of enrolement. The dosage regimen in the studies was clarithromycin 500 mg b.i.d. plus omeprazole 20 mg b.i.d. plus amoxicillin 1 gram b.i.d. for 10 days. In Studies 126 and 127, patients who took the omeprazole regimen also received an additional 18 days of omeprazole 20 mg q.d. Endpoints studied were eradication of *H. pylori* and duodenal ulcer healing (studies 126 and 127 only). *H. pylori* status was determined by CLOtest®, histology, and culture in all three studies. For a given patient, *H. pylori* was considered eradicated if at least two of these tests were negative, and none was positive. The combination of clarithromycin plus omeprazole and amoxicillin was effective in eradicating *H. pylori*.

**Per-Protocol and Intent-To-Treat *H. pylori* Eradication Rates**
**% of Patients Cured [95% Confidence Interval]**

| | Clarithromycin + omeprazole + amoxicillin | | Clarithromycin + amoxicillin | |
|---|---|---|---|---|
| | Per-Protocol† | Intent-To-Treat‡ | Per-Protocol† | Intent-To-Treat‡ |
| Study 126 | *77 [64, 86] (n=64) | 69 [57, 79] (n = 80) | 43 [31, 56] (n = 67) | 37 [27, 48] (n = 84) |
| Study 127 | *78 [67, 88] (n=65) | 73 [61, 82] (n = 77) | 41 [29, 54] (n = 68) | 36 [26, 47] (n = 84) |
| Study M96-446 | *90 [80, 96] (n = 69) | 83 [74, 91] (n = 84) | 33 [24, 44] (n = 93) | 32 [23, 42] (n = 99) |

† Patients were included in the analysis if they had confirmed duodenal ulcer disease (active ulcer studies 126 and 127; history of ulcer within 5 years, study M96-446) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology, and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy. The impact of eradication on ulcer recurrence has not been assessed in patients with a past history of ulcer.

‡ Patients were included in the analysis if they had documented *H. pylori* infection at baseline and had confirmed duodenal ulcer disease. All dropouts were included as failures of therapy.

* $p < 0.05$ versus clarithromycin plus amoxicillin.

*Safety:*

In clinical trials using combination therapy with clarithromycin plus omeprazole and amoxicillin, no adverse reactions peculiar to the combination of these drugs have been observed. Adverse reactions that have occurred have been limited to those that have been previously reported with clarithromycin, omeprazole, or amoxicillin.

The most frequent adverse experiences observed in clinical trials using combination therapy with clarithromycin plus omeprazole and amoxicillin (n=274) were diarrhea (14%), taste perversion (10%), and headache (7%).

For information about adverse reactions with omeprazole or amoxicillin, refer to the ADVERSE REACTIONS section of their package inserts.

**Clarithromycin + Omeprazole Therapy**

Four randomized, double-blind, multi-center studies (067, 100, 812b, and 058) evaluated clarithromycin 500 mg t.i.d. plus omeprazole 40 mg q.d. for 14 days, followed by omeprazole 20 mg q.d. (067, 100, and 058) or by omeprazole 40 mg q.d. (812b) for an additional 14 days in patients with active duodenal ulcer associated with *H. pylori*. Studies 067 and 100 were conducted in the U.S. and Canada and enrolled 242 and 256 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 219 patients in Study 067 and 228 patients in Study 100. These studies compared the combination regimen to omeprazole and clarithromycin monotherapies. Studies 812b and 058 were conducted in Europe and enrolled 154 and 215 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 148 patients in

Study 812b and 208 patients in Study 058. These studies compared the combination regimen to omeprazole monotherapy. The results for the efficacy analyses for these studies are described below.

*Duodenal Ulcer Healing:*
The combination of clarithromycin and omeprazole was as effective as omeprazole alone for healing duodenal ulcer.

**End-of-Treatment Ulcer Healing Rates**
**Percent of Patients Healed (n/N)**

| Study | Clarithromycin + Omeprazole | Omeprazole | Clarithromycin |
|---|---|---|---|
| **U.S. Studies** | | | |
| **Study 100** | 94% (58/62)† | 88% (60/68) | 71% (49/69) |
| **Study 067** | 88% (56/64)† | 85% (55/65) | 64% (44/69) |
| **Non-U.S. Studies** | | | |
| **Study 058** | 99% (84/85) | 95% (82/86) | N/A |
| **Study 812b**[1] | 100% (64/64) | 99% (71/72) | N/A |

† $p<0.05$ for clarithromycin + omeprazole versus clarithromycin monotherapy.
[1] In Study 812b patients received omeprazole 40 mg daily for days 15 to 28.

*Eradication of H. pylori Associated with Duodenal Ulcer:*
The combination of clarithromycin and omeprazole was effective in eradicating *H. pylori.*

***H. pylori* Eradication Rates (Per-Protocol Analysis) at 4 to 6 weeks**
**Percent of Patients Cured (n/N)**

| Study | Clarithromycin + Omeprazole | Omeprazole | Clarithromycin |
|---|---|---|---|
| **U.S. Studies** | | | |
| **Study 100** | 64% (39/61)†‡ | 0% (0/59) | 39% (17/44) |
| **Study 067** | 74% (39/53)†‡ | 0% (0/54) | 31% (13/42) |
| **Non-U.S. Studies** | | | |
| **Study 058** | 74% (64/86)‡ | 1% (1/90) | N/A |
| **Study 812b** | 83% (50/60)‡ | 1% (1/74) | N/A |

† Statistically significantly higher than clarithromycin monotherapy ($p<0.05$).
‡ Statistically significantly higher than omeprazole monotherapy ($p<0.05$).

*H. pylori* eradication was defined as no positive test (culture or histology) at 4 weeks following the end of treatment, and two negative tests were required to be considered eradicated. In the per-protocol analysis, the following patients were excluded: dropouts, patients with major protocol violations, patients with missing *H. pylori* tests post-treatment, and patients that were not assessed for *H. pylori* eradication at 4 weeks after the end of treatment because they were found to have an unhealed ulcer at the end of treatment.

Ulcer recurrence at 6-months following the end of treatment was assessed for patients in whom ulcers were healed post-treatment.

**Ulcer Recurrence at 6 months by *H. pylori* Status at 4-6 Weeks**

| | *H. pylori* Negative | *H. pylori* Positive |
|---|---|---|
| **U.S. Studies** | | |
| **Study 100** | | |
| Clarithromycin + Omeprazole | 6% (2/34) | 56% (9/16) |
| Omeprazole | - (0/0) | 71% (35/49) |
| Clarithromycin | 12% (2/17) | 32% (7/22) |
| **Study 067** | | |
| Clarithromycin + Omeprazole | 38% (11/29) | 50% (6/12) |
| Omeprazole | - (0/0) | 67% (31/46) |
| Clarithromycin | 18% (2/11) | 52% (14/27) |
| **Non-U.S. Studies** | | |
| **Study 058** | | |
| Clarithromycin + Omeprazole | 6% (3/53) | 24% (4/17) |
| Omeprazole | 0% (0/3) | 55% (39/71) |
| **Study 812b*** | | |
| Clarithromycin + Omeprazole | 5% (2/42) | 0% (0/7) |
| Omeprazole | 0% (0/1) | 54% (32/59) |
| ***12-month recurrence rates:** | | |
| Clarithromycin + Omeprazole | 3% (1/40) | 0% (0/6) |
| Omeprazole | 0% (0/1) | 67% (29/43) |

Thus, in patients with duodenal ulcer associated with *H. pylori* infection, eradication of *H. pylori* reduced ulcer recurrence.

*Safety:*
The adverse event profiles for the four studies showed that the combination of clarithromycin 500 mg t.i.d. and omeprazole 40 mg q.d. for 14 days, followed by omeprazole 20 mg q.d. (067, 100, and 058) or 40 mg q.d. (812b) for an additional 14 days was well tolerated. Of the 346 patients who received the combination, 12 (3.5%) patients discontinued study drug due to adverse events.

**Adverse Events with an Incidence of 3% or Greater**

| Adverse Event | Clarithromycin + Omeprazole (N = 346) % of Patients | Omeprazole (N = 355) % of Patients | Clarithromycin (N = 166) % of Patients* |
|---|---|---|---|
| Taste Perversion | 15% | 1% | 16% |
| Nausea | 5% | 1% | 3% |
| Headache | 5% | 6% | 9% |
| Diarrhea | 4% | 3% | 7% |
| Vomiting | 4% | <1% | 1% |
| Abdominal Pain | 3% | 2% | 1% |
| Infection | 3% | 4% | 2% |

* Studies 067 and 100, only

Most of these events were mild to moderate in severity.

*Changes in Laboratory Values:*
Changes in laboratory values with possible clinical significance in patients taking clarithromycin and omeprazole were as follows:

Hepatic - elevated direct bilirubin <1%; GGT <1%; SGOT (AST) <1%; SGPT (ALT) <1%.

Renal - elevated serum creatinine <1%.

For information on omeprazole, refer to the ADVERSE REACTIONS section of the PRILOSEC package insert.

**Clarithromycin + Ranitidine Bismuth Citrate Therapy**
In a U.S. double-blind, randomized, multicenter, dose-comparison trial, ranitidine bismuth citrate 400 mg b.i.d. for 4 weeks plus clarithromycin 500 mg b.i.d. for the first 2 weeks was found to have an equivalent *H. pylori* eradication rate (based on culture and histology) when compared to ranitidine bismuth citrate 400 mg b.i.d. for 4 weeks plus clarithromycin 500 mg t.i.d. for the first 2 weeks. The intent-to-treat *H. pylori* eradication rates are shown below:

**H. pylori Eradication Rates in Study H2BA-3001**

| Analysis | RBC 400 mg + Clarithromycin 500 mg b.i.d. | RBC 400 mg + Clarithromycin 500 mg t.i.d. | 95% CI Rate Difference |
|---|---|---|---|
| ITT | 65% (122/188) [58%, 72%] | 63% (122/195) [55%, 69%] | (-8%, 12%) |
| Per-Protocol | 72% (117/162) [65%, 79%] | 71% (120/170) [63%, 77%] | (-9%, 12%) |

*H. pylori* eradication was defined as no positive test at 4 weeks following the end of treatment. Patients must have had two tests performed, and these must have been negative to be considered eradicated of *H. pylori*. The following patients were excluded from the per-protocol analysis: patients not infected with *H. pylori* prestudy, dropouts, patients with major protocol violations, patients with missing *H. pylori* tests. Patients excluded from the intent-to-treat analysis included those not infected with *H pylori* prestudy and those with missing *H. pylori* tests prestudy. Patients were assessed for *H. pylori* eradication (4 weeks following treatment) regardless of their healing status (at the end of treatment).

The relationship between *H. pylori* eradication and duodenal ulcer recurrence was assessed in a combined analysis of six U.S. randomized, double-blind, multicenter, placebo-controlled trials using Tritec with or without antibiotics. The results from approximately 650 U.S. patients showed that the risk of ulcer recurrence within 6 months of completing treatment was two times less likely in patients whose *H. pylori* infection was eradicated compared to patients in whom *H. pylori* infection was not eradicated.

*Safety*:
In clinical trials using combination therapy with clarithromycin plus ranitidine bismuth citrate, no adverse reactions peculiar to the combination of these drugs (using clarithromycin twice daily or three times a day) were observed. Adverse reactions that have occurred have been limited to those reported with clarithromycin or ranitidine bismuth citrate. (See **ADVERSE REACTIONS** section of the Tritec package insert.) The most frequent adverse experiences observed in clinical trials using combination therapy with clarithromycin (500 mg three times a day) with ranitidine bismuth citrate (n = 329) were taste disturbance (11%), diarrhea (5%), nausea and vomiting (3%). The most frequent adverse experiences observed in clinical trials using combination therapy with clarithromycin (500 mg twice daily) with ranitidine bismuth citrate (n = 196) were taste disturbance (8%), nausea and vomiting (5%), and diarrhea (4%).

## ANIMAL PHARMACOLOGY AND TOXICOLOGY

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 to 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 $mg/m^2$). Renal tubular degeneration (calculated on a $mg/m^2$ 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 $mg/m^2$ 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 $mg/m^2$ 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 $mg/m^2$ 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.

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APPROVAL (AP)

**APPEARS THIS WAY ON ORIGINAL**