Biaxin advertisement.

[s.l.]: [s.n.], 1995

NEW

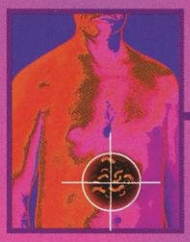
BIAXIN AND OMEPRAZOLE REGIMEN

A POWERFUL ATTACK ON ACTIVE DUODENAL ULCER DISEASE

Helicobacter pylori

BIAXIN®
clarithromycin
Tablets

SEE BIAXIN (ACCOMPANYING) BRIEF SUMMARY
AND PRILOSEC FULL PRESCRIBING INFORMATION.



A POWERFUL ATTACK

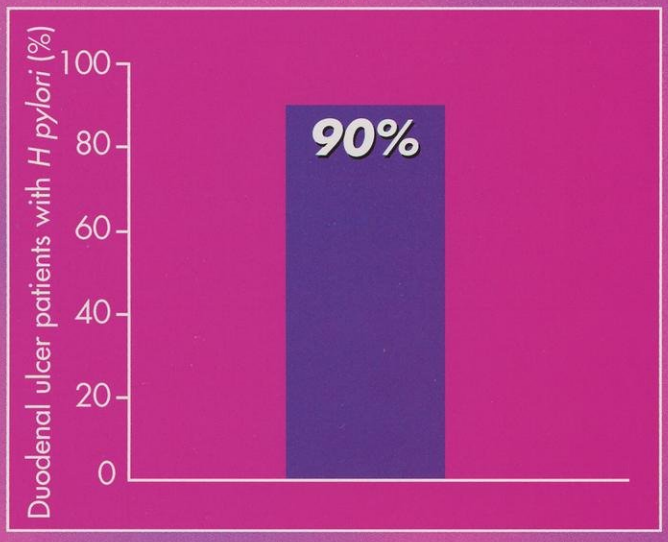
H PYLORI AND ACTIVE DUODENAL ULCER DISEASE

- **Whom to Treat—NIH Consensus[1]**

  "All patients with duodenal ulcers who are infected with *H pylori* should be treated with antimicrobials..."

- **90% of Duodenal Ulcer Patients Are Infected With *H pylori*[2]**

Percentage of duodenal ulcer patients with *H pylori* infection[2]



- **Duodenal Ulcers Recur Within 12 Months in Up to 90% of Patients After Discontinuation of Antisecretory Therapy[3]**
- **Eradication of *H pylori* Has Been Demonstrated to Reduce the Risk of Duodenal Ulcer Recurrence[4]**

SEE BIAXIN (ACCOMPANYING) BRIEF SUMMARY AND PRILOSEC FULL PRESCRIBING INFORMATION.

THE BIAXIN® AND PRILOSEC® REGIMEN (omeprazole)

NEW

HEAL

Active Duodenal Ulcer*

BIAXIN/PRILOSEC patients: 94% (58/62) and 88% (56/64) in U.S. studies and 99% (84/85) and 100% (64/64) in non-U.S. studies.[†4]

ERADICATE

H pylori Infection‡

BIAXIN/PRILOSEC patients: 64% (39/61) and 74% (39/53) at 4-6 weeks post-treatment in U.S. studies and 74% (64/86) and 83% (50/60) at 4-6 weeks in non-U.S. studies. In patients who fail therapy, susceptibility testing should be done if possible. If resistance is demonstrated, alternative therapy is recommended.[4]

and

PREVENT

Ulcer Recurrence*

BIAXIN/PRILOSEC patients with *H pylori* eradication: 6% (2/34) and 38% (11/29) in U.S. studies and 6% (3/53) and 5% (2/42) in non-U.S. studies. BIAXIN/PRILOSEC patients without *H pylori* eradication: 56% (9/16) and 50% (6/12) in U.S. studies and 24% (4/17) and 0% (0/7) in non-U.S. studies.[4]

BIAXIN®
clarithromycin
Tablets

* Determined by endoscopy
† In one study patients received PRILOSEC 40 mg daily for days 15-28
‡ Determined by histology, culture, and an experimental test

A POWERFUL ATTACK— THE BIAXIN® AND PRILOSEC® REGIMEN

(omeprazole)

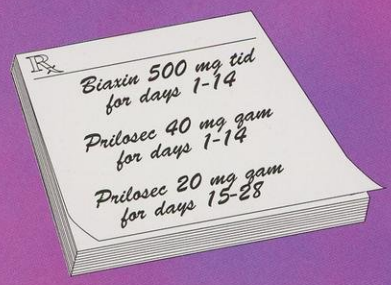
VERY WELL-TOLERATED REGIMEN

- Low incidence of adverse events including taste perversion (15%), nausea (5%), headache (5%), diarrhea (4%), vomiting (4%), abdominal pain (3%), or infection (3%).[4]
- Clarithromycin should not be used in pregnant women except in circumstances where no alternative therapy is appropriate.[4]
- Clarithromycin should not be used in patients receiving terfenadine who have pre-existing cardiac abnormalities or electrolyte disturbances.[4]

EASY-TO-FOLLOW REGIMEN[4]

Days 1-14	**BIAXIN** 500 mg tid **PRILOSEC** 40 mg qam
Days 15-28	**PRILOSEC** 20 mg qam

- BIAXIN in combination with PRILOSEC is indicated for the treatment of patients with an active duodenal ulcer associated with *H pylori* infection. The eradication of *H pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence. In patients who fail therapy, susceptibility testing should be done if possible. If resistance is demonstrated, alternative therapy is recommended.[4]



SEE BIAXIN (ACCOMPANYING) BRIEF SUMMARY AND PRILOSEC FULL PRESCRIBING INFORMATION.

References
1. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. *JAMA.* 1994;272:65-69. 2. Marshall BJ. *Helicobacter pylori. Am J Gastro.* 1994;89:S116-S128. 3. Sloane R, Cohen H. Common-sense management of *Helicobacter pylori*-associated gastroduodenal disease. *Gastroenterol Clin North Am* 1993;22:199-206. 4. Biaxin package insert, Abbott Laboratories.

BIAXIN® clarithromycin Tablets

Abbott Laboratories
North Chicago, IL 60064

503-022-4502A
Printed in U.S.A.

BRIEF SUMMARY

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

BIAXIN® Filmtab®

(clarithromycin tablets)

BIAXIN® Granules

(clarithromycin for oral suspension)

INDICATIONS AND USAGE

BIAXIN (clarithromycin) Filmtab tablets in combination with PRILOSEC (omeprazole) capsules is indicated for the treatment of patients with an active duodenal ulcer associated with *H. pylori* infection. The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence.

In patients who fail therapy, susceptibility testing should be done if possible. If resistance is demonstrated, alternative therapy is recommended.

CONTRAINDICATIONS

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

Clarithromycin is contraindicated in patients receiving terfenadine therapy who have preexisting cardiac abnormalities (arrhythmia, bradycardia, QT interval prolongation, ischemic heart disease, congestive heart failure, etc.) or electrolyte disturbances. (See **PRECAUTIONS-***Drug Interactions*.)

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

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 on omeprazole, refer to the WARNINGS section of the PRILOSEC package insert.

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.

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

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. The increase in the QT interval seen in association with the elevated terfenadine acid metabolite level is unlikely to be of clinical significance in healthy individuals. Clarithromycin should not be given to patients receiving terfenadine therapy who have preexisting cardiac abnormalities (arrhythmia, bradycardia, QT interval prolongation, ischemic heart disease, congestive heart failure, etc.) or electrolyte disturbances. (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.

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.

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 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.

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, hexobarbital, phenytoin, alfentanil, disopyramide, lovastatin, bromocriptine, valproate, terfenadine, cisapride, pimozide, 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 children under 6 months of age have not been established. 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

See **Clinical Studies** - *Safety*

Post-Marketing Experience:

Allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis and Stevens-Johnson syndrome have occurred. Other spontaneously reported adverse events include glossitis, stomatitis, oral moniliasis, vomiting and dizziness. 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 have also been reported.

Transient CNS events including behavioral changes, confusional states, depersonalization, disorientation, hallucinations, insomnia, nightmares, tinnitus, and vertigo have been reported during post-marketing surveillance. Events usually resolve quickly 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.

Rarely, erythromycin and clarithromycin have been associated with ventricular arrhythmias, including ventricular tachycardia and torsades de pointes, in individuals with prolonged QT_C intervals.

Changes in Laboratory Values - See **Clinical Studies**

CLINICAL STUDIES

Duodenal Ulcer Associated with *H. pylori* Infection

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.

Filmtab - Film-sealed tablets, Abbott
Ref. 03-4659-R9-Revised: April, 1996

Abbott Laboratories
North Chicago, IL 60064, U.S.A.
606-022-6821 **MASTER**
Printed in U.S.A.