

BIAXIN™

(Clarithromycin)

Filmab Tablets

BRIEF SUMMARY

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INDICATIONS AND USAGE

BIAXIN (Clarithromycin) is indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below

Upper Respiratory Tract Infections

Pharyngitis/Tonsillitis due to *Streptococcus pyogenes*

Acute maxillary sinusitis due to *Streptococcus pneumoniae*

Lower Respiratory Tract Infections

Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae*

Moraxella catarrhalis or *Streptococcus pneumoniae*

Pneumonia due to *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*

Uncomplicated Skin and Skin Structure Infections due to *Staphylococcus aureus* or *Streptococcus pyogenes*. Abscesses usually require surgical drainage

Protein supplementation, and treatment with an antibacterial drug effective against *Clostridium difficile*

CONTRAINDICATIONS

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

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 ON 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.)

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

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 effective against *Clostridium difficile*.

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 intervals may be appropriate.

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 mg or 500 mg q 12 h clarithromycin), the steady-state levels of Cmax, Cmin, and the area under the serum concentration time curve (AUC) increased about 20%.

Single-dose administration of clarithromycin has been shown to result in increased concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered.

The following drug interactions have not been reported in clinical trials with clarithromycin: however, they have been observed with erythromycin products.

Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin levels.

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly.

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

Erythromycin has been reported to decrease the clearance of triazolam and thus may increase the pharmacologic effect of triazolam.

The use of erythromycin 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 with carbamazepine, cyclosporine, theophylline, and phenytoin. Serum concentrations of drugs metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The following in vitro mutagenicity tests have been conducted with clarithromycin.

Salmonella/Mammalian Microsome Test

Bacterial Induced Mutation Frequency Test

In Vitro Chromosome Aberration Test

Rat Hepatocyte DNA Synthesis Assay

Mouse Lymphoma Assay

Mouse Dominant Lethal Assay

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

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

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

Long term studies in animals have not been performed to evaluate carcinogenic potential.

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 or intravenous doses of 30 mg/kg/day administered during gestation days 6 to 18) failed to demonstrate any teratogenicity from clarithromycin. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6 to 15. Plasma levels after 150 mg/kg/day were 2 times the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day during gestation days 6 to 15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day exposure resulted in plasma levels 7 times the human serum levels. In monkeys, an oral dose of 70 mg/kg/day produced fetal growth retardation at plasma levels that were 2 times the human serum levels.

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.

Pediatric Use: Safety and effectiveness of clarithromycin in children under 12 years of age have not been established.

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 concentrations of clarithromycin and 14-OH clarithromycin were increased. The AUC was also increased. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients. Dosage adjustment should be considered in the 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 patients discontinued therapy because of drug-related side effects.

The most frequently reported events, whether drug-related or not were diarrhea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% were described as severe.

In studies of pneumonia 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.

The following adverse events have been reported with erythromycin products but not in clinical trials of clarithromycin.

Rarely, erythromycin has been associated with ventricular arrhythmias, including ventricular tachycardia and torsades de pointes, in individuals with prolonged QT intervals.

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%, and total bilirubin < 1%.

Hematologic: Decreased WBC < 1%, and elevated prothrombin time 1%. Renal: Elevated BUN 4%, and elevated serum creatinine < 1%.

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Reviews

Reviews of books for this section are welcomed from osteopathic physicians and from faculty members in osteopathic medical institutions. Interested individuals will be sent information on format on request. A certain number of reviews are invited for books supplied to JAOA by publishers; persons wishing to be part of this program should write to the editors, giving background and areas of interest.

From Early Osteopathy in the Words of A.T. Still

Edited by R.V. Schnucker. Pp 382, with illus. Thomas Jefferson University Press, LB 115 NMSU, 63501, 1991, \$80.

This fascinating and unusual book was published just as our profession was about to celebrate its 100th anniversary. Several years ago, when I was a good deal younger, a student came to me and asked, "Tell me, Dr Northup, what was Dr Still like?" This question has intrigued me ever since that time.

This collection of Dr Still's thoughts and writings tells me more about the man himself than some latter-day biographies, regardless of how objective they might be. He was a brilliant medical observer who was intensely dissatisfied with the status of medical practice of his time. Dr Still's writings are a testament to his original thinking and his opposition

to many of the current forms of treatment of his day.

From Early Osteopathy in the Words of A.T. Still is the type of book from which one can gain much insight and enjoyment, just by browsing through its pages. I highly recommend it for leisure reading; although measuring 11 inches × 9 inches, this book is scarcely one to be read in bed!

GEORGE W. NORTHUP, DO
Editor Emeritus

Osteopathy—Research and Practice

By A.T. Still. Pp 293. Eastland Press, PO Box 12689, Seattle, WA 98111, 1992, \$34.95.

A resurgence of interest in Andrew Taylor Still's writings occurred during our centennial year, 1992. In the latter part of 1991, a new biography of "The Old Doctor" appeared—the first in more than 50 years. Three additional volumes followed: one dealing with the life and times of the Still family; A.T. Still's writings from *the Journal of Osteopathy*; and the history of the first school of osteopathic medicine. All of these fine books were published by the Thomas Jefferson University Press in Kirksville, Mo.

In 1992, Eastland Press made available this reprinting of *Osteopathy—Research and Practice*, originally published by the author himself in 1910. This modestly priced

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