

# BIAXIN™

(Clarithromycin)

Flimab® 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.

## 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.

Concomitant use of erythromycin 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 itraconazole and thus may increase the pharmacologic effect of itraconazole.

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, hexobarbital, 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 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 150-150 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 only after 150 mg/kg/day, clarithromycin was shown to produce embryonic loss in monkeys. This effect has been attributed to 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 616 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 135 mg/kg/day or intravenous doses of 30 mg/kg/day administered during gestation days 6 to 18) failed to demonstrate any teratogenicity from clarithromycin. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6 to 15. Plasma levels after 150 mg/kg/day were 2 times the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day during gestation days 6 to 15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day exposure resulted in plasma levels 17 times the human serum levels. In monkeys, an oral dose of 70 mg/kg/day produced fetal growth retardation at plasma levels that were 2 times the human serum levels.

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 (2%), abnormal taste (2%), 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%.

Revised, April 1992

References: 1. Data on file, Abbott Laboratories. 2. Kennedy DW, Shihara AH. Sinusitis. In: *Handbook of Current Therapy* 1990. Philadelphia: J.B. Saunders; 1990:187-189. 3. Gault NM. Outpatient management of bacterial lower respiratory tract infections. *Drug Therapy*. March 1990;51:58. 4. Raff MJ, Ramirez JA. Lower respiratory tract infections: A brief review. *Infections in Medicine*. August 1991;45:45-58. 5. Fraschetti F, Scaglione F, Pittet C, Macarone G, Macarone G, Dogan S, Demarini G. The diffusion of clarithromycin and erythromycin into nasal mucus, tonsil and lung in humans. *J Antimicrob Chemother*. 1991;27 (suppl A):61-65. 6. Gupta S, Northcutt VJ, Prokocimer P, Craft JC. Comparative efficacy and safety of clarithromycin and ampicillin in the treatment of acute bacterial exacerbations of chronic bronchitis (Abstract). Presented at the 30th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, October 1990, Atlanta, GA. 7. Kama P, Pukander J, Penttilä M, et al. The comparative efficacy and safety of clarithromycin and ampicillin in the treatment of outpatients with acute maxillary sinusitis. *J Antimicrob Chemother*. 1991;27 (suppl A):83-90.

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## editorial comments

By the time adolescents reach 18 years of age, they have developed their sexual identity. This identity becomes stronger with sexual experience, according to researchers at the Adolescent Health Program, University of Minnesota Hospital and Clinics, Minneapolis.

Using a voluntary, anonymous, confidential survey, researchers examined the sexual orientation of 34,706 students in grades 7 to 12 (49.8% male; 50.2% female). The students represented various ethnic, geographic, and socioeconomic backgrounds. Respondents were asked questions regarding their sexual orientation, fantasies, and behavior.

Overall, 10.7% of the surveyed students were unsure of their sexual orientation; 88.2% said they were totally or predominantly heterosexual, with 1.1% describing themselves as bisexual or predominantly homosexual. Particularly among boys, religious beliefs were correlated with dimensions of homosexuality: 59% of the homosexual boys and 23% of the bisexual boys identified themselves as "not at all religious."

With age, students become more sure of their sexual preference: 25.9% of those 12-year-olds surveyed considered themselves unsure about their sexual preference, compared with 5% of the 18-year-old students.

Complete results are published in the April issue of *Pediatrics*.

Cigarette advertising should be banned throughout the world, recommended officials attending a United Nations-sponsored health conference in early April.

Although smoking in Western countries has declined in recent years, more persons in developing countries are lighting up.

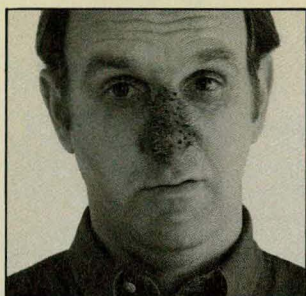
"The tobacco industry sees that it is losing clients in the developed countries, so it is trying to get more clients in the developing countries," said Jorge Pilheu, chairman of the 8th World Conference on Tobacco OR Health. "It is doing that through advertising," said Pilheu.

The World Health Organization estimates that cigarette smoking in Third World countries is increasing by more than 2% annually. In these nations, 40% to 60% of the men and 2% to 10% of the women smoke.

Although conference attendees noted that tobacco advertisers are targeting their message to women in developing countries, US Surgeon General Antonia Novello, MD, criticized the companies' targeting of children. In particular, R. J. Reynold's cartoon

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## Antihistamines can have an overwhelming effect on sinusitis.

**GUAIFED®** Capsules  
(pseudoephedrine HCl 120 mg  
and guaifenesin 250 mg)

**GUAIFED-PD®** Capsules  
(pseudoephedrine HCl 60 mg  
and guaifenesin 300 mg)

### Brief Summary

**CONTRAINDICATIONS:** This product is contraindicated in patients with a known hypersensitivity to any of its ingredients. Also contraindicated in patients with severe hypertension, severe coronary artery disease and patients on MAO inhibitor therapy. Should not be used during pregnancy or in nursing mothers.

Considerable caution should be exercised in patients with hypertension, diabetes mellitus, ischemic heart disease, hyperthyroidism, increased intraocular pressure and prostatic hypertrophy. The elderly (60 years or older) are more likely to exhibit adverse reactions. At dosages higher than the recommended dose, nervousness, dizziness or sleeplessness may occur.

**PRECAUTIONS: General:** Caution should be exercised in patients with high blood pressure, heart disease, diabetes or thyroid disease and in patients who exhibit difficulty in urination due to enlargement of the prostate gland. Check with a physician if symptoms do not improve within 7 days or if accompanied by high fever, rash or persistent headache.

**Drug Interactions:** Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting a physician. MAO inhibitors and beta adrenergic blockers may increase the effect of sympathomimetics. Sympathomimetics may reduce the antihypertensive effects of methyldopa, mecamylamine, reserpine and veratrum alkaloids. Pseudoephedrine hydrochloride may increase the possibility of cardiac arrhythmias in patients presently taking digitalis glycosides.

**Pregnancy:** Pregnancy Category B. It has been shown that pseudoephedrine hydrochloride can cause reduced average weight, length, and rate of skeletal ossification in the animal fetus.

**Nursing Mothers:** Pseudoephedrine is excreted in breast milk; use by nursing mother is not recommended because of the higher than usual risk of side effects from sympathomimetic amines for infants, especially newborn and premature infants.

**Geriatrics:** Pseudoephedrine should be used with caution in the elderly because they may be more sensitive to the effects of the sympathomimetics.

**WARNINGS:** Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician. This medication should be taken a few hours prior to bedtime to minimize the possibility of sleeplessness. Take this medication with a glass of water after each dose, to help loosen mucus in the lungs.

**ADVERSE REACTIONS:** Adverse reactions include nausea, cardiac palpitations, increased irritability or excitement, headache, dizziness, tachycardia, diarrhea, drowsiness, stomach pain, seizures, slowed heart rate, shortness of breath and/or troubled breathing.

**DOSAGE AND ADMINISTRATION: GUAIFED® CAPSULES** Adults and children over 12 years of age: 1 capsule every 12 hours.

**GUAIFED-PD® CAPSULES** Adults and children over 12 years of age: 1 or 2 capsules every 12 hours. Children 6 to 12 years of age: 1 capsule every 12 hours.

**CAUTION: FEDERAL (U.S.A.) LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION.**

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## editorial comments

(continued)

character "Old Joe Camel" came under fire. Always with a cigarette in his mouth, this character is depicted living life in the fast lane.

In addressing this conference, Dr Novello reiterated comments she had made at a March 9 news conference in Washington, DC. At the latter conference, Dr Novello had called on retailers to remove any promotional material with the "Old Joe" character.

"Calling for the voluntary withdrawal of a successful advertising campaign is not a traditional role of organized medicine," commented Dr Novello at the Washington, DC, conference. "Yet, it is the only responsible position that physicians must take regarding these advertisements."

**Acellular pertussis vaccine can be administered for the fourth and fifth doses of the diphtheria-tetanus-pertussis vaccination, recommends the American Academy of Pediatrics (AAP).**

The AAP's statement, which appears in the April issue of *AAP News*, recommends that all infants continue to be immunized with the whole-cell vaccine for the initial three shots of pertussis vaccine.

Although the Academy statement noted that either

acellular or whole-cell vaccines may be used for the fourth and fifth doses, fewer side effects have been reported with the use of the acellular vaccine.

The vaccination schedule remains the same, regardless of which vaccine is used. However, the whole-cell pertussis vaccine is the only vaccine that should be administered for the first three doses in children at 2, 4, and 6 months of age, as well as in children who are only partially immunized by age 15 months or older.

To date, Acel-Immune® ( Lederle Laboratories, Wayne, NJ) is the only licensed vaccine approved by the Food and Drug Administration for this use.

**Commercial weight loss products and programs don't work for most consumers, according to a national panel of health experts.**

The 13-member panel, headed by *Annals of Internal Medicine* editor Suzanne W. Fletcher, MD, found that 90% to 95% of dieters regain all or most of their shed pounds within 5 years. Panel members also reviewed evidence indicating a relationship exists between weight loss and increased death rates.

They also found disconcerting the large numbers of normal-weight persons, particu-

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larly women, who are trying to lose weight.

Only voluntary means of weight loss, including appetite suppressants and medically supervised liquid diets, were examined. The panel did not consider dietary changes such as reducing fat intake and red meat consumption, reports the April 2 issue of the *Chicago Tribune*.

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**Fetal alcohol syndrome (FAS) affects an estimated 1 in 99 Native American children born in the United States, reports the March 23/30 issue of *American Medical News*. In the general population, FAS affects 1 in 600 to 1 in 700 children.**

Because of the high incidence among Native Americans, Rep Ben Nighthorse Campbell (D, Colo) has sponsored a bill intended to prevent and treat FAS among Native Americans. If passed, the Comprehensive Indian Fetal Alcohol Syndrome Prevention and Treatment Act would grant federal money (\$10 million for fiscal years 1993 through 1995, with \$15 million for 5 years thereafter) to Indian tribes. This money would be used to develop and

provide community FAS training, education, and prevention programs.

According to the National Council on Alcoholism and Drug Dependence, FAS is the leading cause of mental retardation in the United States.

"Once the child is born ... the damage is there for good," said Robin LaDue, PhD, in addressing the House Committee on Interior and Insular Affairs. A clinical psychologist, Dr LaDue is on staff at the fetal alcohol and drug unit at the University of Washington.

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**Patients with questions regarding breast implants may seek information from an educational and referral program established by the American Society of Plastic and Reconstructive Surgeons (ASPRS).**

In addition, those patients who may be unwilling or unable to speak with their physician or who may be unable to pay for services, can also use this program. Primary care physicians and other nonplastic surgery specialists may use the program as well.

"We have been approached around the country by physicians who are asking us for

help with their patients," says ASPRS President Norman Cole, MD.

The program features the following services:

- A videotape (\$40) and transcript (\$20) of a teleconference featuring a panel of experts—plastic surgeons, oncologists, radiologists—is available from the society by calling (800) 766-4955.
- A free pamphlet addressing common questions patients have concerning their implants can be ordered by leaving a message at (800) 945-6380. Physicians may also order a technically oriented brochure detailing recommendations made by the Food and Drug Administration by calling the same toll-free number.
- Patients who are unwilling or unable to speak with their surgeon may contact a referral network ([800] 635-0635). Although callers will receive a consultation by telephone, if the physician on the other end of the line deems this consultation insufficient, the practitioner will see the caller in person at no charge.

"Each individual is going to be evaluated individually, and no one will be turned away who is in need of treatment," says Dr Cole.