

## CLINICAL CAPSULES

## Statin-Associated Rhabdomyolysis

The risk of rhabdomyolysis is relatively low for the three most frequently prescribed statins—atorvastatin, pravastatin, and simvastatin—but is 10 times higher for cerivastatin, which was taken off the market in August 2001. The risk is more than 5 times higher for fibrates than for statin monotherapy and 12 times higher if the two therapies are combined. Combining cerivastatin with fibrates raises the risk 1,400-fold.

These are some of the conclusions of “the first comprehensive study of rhab-

domyolysis incidence associated with statin and fibrate therapy.” The study involved 252,460 patients who began treatment between 1998 and 2001 at 11 medical centers across the United States, reported David J. Graham, M.D., of the Food and Drug Administration, Rockville, Md., and his associates (JAMA 2004;292:2585-90).

Risk increased sharply among older patients and those with diabetes. The number of patients who needed to be treated per year for 1 case of rhabdomyolysis to develop was nearly 228,000 for monotherapy with the three major statins, compared

with 1 case per 484 for older patients who also had diabetes who took statins plus fibrates, and with 1 case in 10 for patients who took cerivastatin plus fibrates, the researchers said.

## Percutaneous PFO Closure After Stroke

Percutaneous closure of a patent foramen ovale is at least as effective as medical therapy in preventing cerebrovascular recurrences among patients whose initial stroke presumably stemmed from the heart condition, according to Stephan Windecker, M.D., and his associates at the University Hospital Bern (Switzerland).

They studied 308 patients treated for

cryptogenic stroke that was thought to be related to patent foramen ovale. A total of 158 patients received treatment with standard vitamin K antagonist or antiplatelet medications, while 150 received percutaneous closure with occlusive devices placed under local anesthesia (J. Am. Coll. Cardiol. 2004;44:750-8).

Overall, percutaneous closure was as effective as medication in preventing recurrent TIA or stroke over 4 years of follow-up. The procedure was significantly better in two subgroups of patients: those in whom the intervention induced complete closure of the foramen ovale (event rate of 6.5%, compared with 22.2% for medical therapy) and those who had a history of multiple strokes or TIAs (event rate of 7.3%, compared with 33.2% for medical therapy). This is the first study to compare the percutaneous procedure with medical treatment, and the results indicate that prospective randomized trials are warranted, the investigators said.

## Take-Along Pill for Atrial Fibrillation

Patients with occasional atrial fibrillation may eventually be able to treat it by taking a single dose of an antiarrhythmic drug that they carry around with them for that purpose, much as angina patients take nitroglycerin when chest pain arises, according to Paolo Alboni, M.D., of Ospedale Civile, Cento, Italy, and his associates.

The feasibility of this “pill-in-the-pocket” approach was assessed in a study of 210 patients with mild or no heart disease whose AF episodes were infrequent and well-tolerated but lasted long enough to prompt the patients to go to emergency rooms. Over a mean follow-up of 15 months, both flecainide and propafenone interrupted palpitations in 534 of 569 AF episodes (94%), usually within 2 hours. Both drugs were effective for every AF episode in 139 of the 165 patients (84%) who had recurrences (N. Engl. J. Med. 2004;351:2384-91).

The mean number of ER visits for AF among the patients dropped from 45.6 to 4.9 per month, and the mean number of AF-related hospitalizations decreased from 15.0 to 1.6 per month. This approach proved feasible and safe, with a high rate of compliance and a very low incidence of adverse effects, the researchers said.

## Biopsy IDs Drug-Induced Myocarditis

For the first time, endomyocardial biopsy was used to identify clozapine-induced hypersensitivity myocarditis in a patient who developed a throat infection, dyspnea, and cardiac enlargement while hospitalized for a schizophrenic break, according to Maurizio Pieroni, M.D., and his associates at San Raffaele Hospital, Milan.

The 27-year-old man was admitted because resistance to his usual neuroleptic therapy had allowed psychotic symptoms to develop. The patient responded within 12 days to clozapine but on the 12th day developed symptoms that suggested either acute viral myocarditis or a hypersensitivity reaction to the drug. Clozapine-induced myocarditis is often fatal, so clozapine therapy was withdrawn, but it was also the best drug to curb the patient's psychosis (Chest 2004;126:1703-5).

Thus “endomyocardial biopsy was crucial to establish a correct diagnosis and appropriate treatment,” they said.

—Mary Ann Moon

Avelox (moxifloxacin) is a registered trademark of Bayer Corp.

**Reference:** 1. Zervas M, Martinez FJ, Amsden GW, Chaudry N. 3-day azithromycin versus 5-day moxifloxacin in outpatients with acute exacerbation of chronic bronchitis (AECB). Poster presented at: 49th International Respiratory Congress (AARC); December 8-11, 2003; Las Vegas, Nev. Poster 184. Data on file, final study report A0661087. Pfizer Inc., New York, NY.

## ZITHROMAX® (azithromycin tablets)

## BRIEF SUMMARY

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZITHROMAX® (azithromycin) and other bacterial drugs, ZITHROMAX (azithromycin) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

## INDICATIONS AND USAGE

ZITHROMAX® (azithromycin) is indicated for the treatment of patients with mild to moderate infections (pneumonia; see **WARNINGS**) caused by susceptible strains of the designated microorganisms in the specific conditions listed below. **As recommended dosages, durations of therapy and applicable patient populations vary among these infections. Please see **DOSAGE AND ADMINISTRATION** for specific dosing recommendations.**

**Adults:** Acute bacterial exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.

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

**Community-acquired pneumonia** due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients appropriate for oral therapy.

**NOTE:** Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

**Pharyngitis/tonsillitis** caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.

**NOTE:** Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX® is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to ZITHROMAX®, susceptibility tests should be performed when patients are treated with ZITHROMAX®. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

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

**Urethritis and cervicitis** due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

**Genital ulcer disease** in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established.

ZITHROMAX®, at the recommended dose, should not be relied upon to treat syphilis. Antimicrobial agents used in high doses for short periods of time to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually-transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with ZITHROMAX® may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZITHROMAX (azithromycin) and other antibacterial drugs, ZITHROMAX (azithromycin) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

## CONTRAINDICATIONS

ZITHROMAX® is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin or any macrolide antibiotic.

## WARNINGS

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported. (See **CONTRAINDICATIONS**.) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

**In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).**

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

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of “antibiotic-associated colitis.”

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

## PRECAUTIONS

**General:** Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. Due to the limited data in subjects with GFR <10 mL/min, caution should be exercised when prescribing azithromycin in these patients.

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization.

Prescribing ZITHROMAX (azithromycin) in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

**Information for Patients:** ZITHROMAX® tablets can be taken with or without food. Patients should also be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin simultaneously.

The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

Patients should be counseled that antibacterial drugs including ZITHROMAX (azithromycin) should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZITHROMAX (azithromycin) is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZITHROMAX (azithromycin) or other antibacterial drugs in the future.

**Drug Interactions:** Co-administration of nefazodone at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nefazodone, close monitoring for known side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted. (See **ADVERSE REACTIONS**.)

Azithromycin did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. When used in therapeutic doses, azithromycin had a modest effect on the pharmacokinetics of atorvastatin, carbamazepine, ceftriaxone, didanosine, efavirenz, fluconazole, indinavir, midazolam, rifabutin, sildenafil, theophylline (intravenous and oral), triazolam, trimethoprim/sulfamethoxazole or zidovudine. Co-administration with efavirenz or fluconazole had a

modest effect on the pharmacokinetics of azithromycin. No dosage adjustment of either drug is recommended when azithromycin is coadministered with any of the above agents.

Interactions with the drugs listed below have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised.

Digoxin—elevated digoxin concentrations. Ergotamine or dihydroergotamine—acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia. Terfenadine, cyclosporine, hexobarbital and phenytoin concentrations.

**Laboratory Test Interactions:** There are no reported laboratory test interactions.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found.

**Pregnancy:** Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (i.e., 200 mg/kg/day). These doses, based on a mg/m<sup>2</sup> basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

**Nursing Mothers:** It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

**Studies evaluating the use of repeated courses of therapy have not been conducted.**

**Geriatric Use:** Pharmacokinetic parameters in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen.

In multiple-dose clinical trials of oral azithromycin, 9% of patients were at least 65 years of age (458/4949) and 3% of patients (144/4949) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ZITHROMAX® 250 mg tablets contain 0.9 mg of sodium per tablet. ZITHROMAX® 500 mg tablets contain 1.8 mg of sodium per tablet.

## ADVERSE REACTIONS

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely. Approximately 0.7% of the patients (adults and pediatric patients) from the 5-day multiple-dose clinical trials discontinued ZITHROMAX (azithromycin) therapy because of treatment-related side effects. In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related side effects was 0.8%. In clinical trials in pediatric patients given 30 mg/kg, either as a single dose or over 3 days, discontinuation from the trials due to treatment-related side effects was approximately 1%. (See **DOSAGE AND ADMINISTRATION**.) Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain.

**Adults:** Multiple-dose regimens: Overall, the most common treatment-related side effects in adult patients receiving multiple-dose regimens of ZITHROMAX® were related to the gastrointestinal system with diarrhea/loose stools (4-5%), nausea (3%) and abdominal pain (2-3%) being the most frequently reported.

No other treatment-related side effects occurred in patients on the multiple-dose regimens of ZITHROMAX® with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

**Cardiovascular:** Palpitations, chest pain. **Gastrointestinal:** Dyspepsia, flatulence, vomiting, melena and cholestatic jaundice. **Genitourinary:** Monilia, vaginitis and nephritis. **Nervous System:** Dizziness, headache, vertigo and somnolence. **General:** Fatigue. **Allergic:** Rash, pruritus, photosensitivity and angioedema.

**Single 1-gram dose regimen:** Overall, the most common side effects in patients receiving a single-dose regimen of ZITHROMAX® were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Side effects that occurred in patients on the single one-gram dosing regimen of ZITHROMAX® with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%) and vaginitis (1%).

**Single 2-gram dose regimen:** Overall, the most common side effects in patients receiving a single 2-gram dose of ZITHROMAX® were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%) and dizziness (1%). The majority of these complaints were mild in nature.

**Post-Marketing Experience:** Adverse events reported with azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship may not be established include:

**Allergic:** Arthralgia, edema, urticaria and angioedema. **Cardiovascular:** Arrhythmias including ventricular tachycardia and hypotension. There have been rare reports of QT prolongation and *torsades de pointes*. **Gastrointestinal:** Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis, pancreatitis, oral candidiasis and rare reports of tongue discoloration. **General:** Asthenia, paresthesia, fatigue, malaise and anaphylaxis (rarely fatal). **Genitourinary:** Interstitial nephritis and acute renal failure and vaginitis.

**Hematopoietic:** Thrombocytopenia. **Liver/Biliary:** Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death. **Nervous System:** Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope. **Psychiatric:** Aggressive reaction and anxiety. **Skin/Appendages:** Pruritus, rarely serious skin reactions including erythema multiforme, Stevens Johnson Syndrome and toxic epidermal necrolysis. **Special Senses:** Hearing disturbances including hearing loss, deafness and/or tinnitus and rare reports of taste perception.

**Laboratory Abnormalities:** **Adults:** Clinically significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows: with an incidence of greater than 1%: decreased hemoglobin, hematocrit, lymphocytes, neutrophils, and blood glucose; elevated serum creatine phosphokinase, potassium, ALT, GGT, AST, BUN, creatinine, blood glucose, platelet count, lymphocytes, neutrophils, and eosinophils; with an incidence of less than 1%: leukopenia, neutropenia, decreased sodium, potassium, platelet count, elevated monocytes, basophils, bicarbonate, serum alkaline phosphatase, bilirubin, LDH and phosphate. The majority of subjects with elevated serum creatinine also had abnormal values at baseline.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 5000 patients, four patients discontinued therapy because of treatment-related liver enzyme abnormalities and one because of a renal function abnormality.

## DOSAGE AND ADMINISTRATION (See INDICATIONS AND USAGE.)

Infection*	Recommended Dose/Duration of Therapy
Community-acquired pneumonia (mild severity)	500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5.
Pharyngitis/tonsillitis (second line therapy)	500 mg QD x 3 days
Skin/skin structure (uncomplicated)	500 mg QD x 3 days
Acute bacterial exacerbations of chronic obstructive pulmonary disease (mild to moderate)	500 mg QD x 3 days
Acute bacterial sinusitis	500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5.
Genital ulcer disease (chancroid)	One single 1 gram dose
Non-gonococcal urethritis and cervicitis	One single 1 gram dose
Gonococcal urethritis and cervicitis	One single 2 gram dose

**\* DUE TO THE INDICATED ORGANISMS (See INDICATIONS AND USAGE.)**

ZITHROMAX® tablets can be taken with or without food.

**Renal Insufficiency:**

No dosage adjustment is recommended for subjects with renal impairment (GFR  $\geq$  80 mL/min). The mean AUC<sub>0-24</sub> was similar in subjects with GFR 10-80 mL/min compared to subjects with normal renal function, whereas it increased 35% in subjects with GFR <10 mL/min compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to subjects with severe renal impairment.

**Hepatic Insufficiency:**

The pharmacokinetics of azithromycin in subjects with hepatic impairment have not been established. No dose adjustment recommendations can be made in patients with impaired hepatic function.

No dosage adjustment is recommended based on age or gender.

For more detailed professional information please refer to the full prescribing information. Rev. 4 January 2004