

# Early Menopause Doubles CVD Risk Later

VITALS

**Major Finding:** Women who had menopause before the age of 46 were 2.1 times more likely to have a cardiovascular disease event later in life, compared with those who did not have early menopause.

**Data Source:** A cohort analysis of 2,509 women in MESA followed for an average of 7 years.

**Disclosures:** The study was funded by the National Heart, Lung, and Blood Institute.

BY DOUG BRUNK

FROM THE ANNUAL MEETING OF THE  
ENDOCRINE SOCIETY

SAN DIEGO — Women who go through menopause before the age of 46 are twice as likely to have a heart attack, stroke, or other cardiovascular event later in life as are women who do not go through early menopause, results from a

large, multiethnic study showed.

“Our study is observational, so we cannot conclude that early menopause somehow causes these cardiovascular disease events, but our findings support using early menopause as a marker of increased cardiovascular disease risk,” Dr. Melissa F. Wellons said during a press briefing at the meeting. “Therefore, getting clinicians to ask

women about menopause and about when they went through menopause is an important part of potentially determining what their risk of CVD is in the future. Doing that can give them information on placing these women with early menopause into a higher risk group and counseling them appropriately, such as encouraging them to stop smoking, exercise, and lose weight.”

Dr. Wellons, a fellow in the department of medicine at the University of Alabama, Birmingham, and her associates evaluated data from 2,509 women enrolled in the observational Multi-Ethnic Study of Atherosclerosis (MESA), funded by the National Institutes of Health. It included more than 6,000 women, from six communities in the United States, who were recruited in 2000 and followed for an average of 7 years. Most (40%) were white, 25% were black, 22%

## Zmax® (azithromycin extended release) for oral suspension

### Brief Summary of Prescribing Information

#### INDICATIONS AND USAGE

Zmax is indicated for the treatment with mild to moderate infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below.

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

**Community-acquired pneumonia** in adults and pediatric patients six months of age or older due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*, in patients appropriate for oral therapy. Pediatric use in this indication is based on extrapolation of adult efficacy.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zmax and other antibacterial drugs, Zmax should be used only to treat 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.

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

#### CONTRAINDICATIONS

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

#### WARNINGS AND PRECAUTIONS

##### Allergic and skin reactions

Serious allergic reactions, including angioedema, anaphylaxis, Stevens Johnson syndrome, and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy using other formulations. Although rare, fatalities have been reported. 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 exposure to antigen has not been determined.

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

##### *Clostridium difficile*-associated diarrhea

*Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Zmax, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hyper toxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

##### Exacerbation of myasthenia gravis

Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy.

##### Gastrointestinal Disturbances

A higher incidence of gastrointestinal adverse events (8 of 19 subjects) was observed when Zmax was administered to a limited number of subjects with GFR <10 mL/min.

##### Prolongation of the QT interval

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.

##### Development of drug resistant bacteria

Prescribing Zmax in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

#### ADVERSE REACTIONS

##### Clinical studies experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

##### Adults:

The data described below reflect exposure to Zmax in 728 adult patients. All patients received a single 2-g oral dose of Zmax. The population studied had community-acquired pneumonia and acute bacterial sinusitis.

In controlled clinical trials with Zmax, the majority of the reported treatment-related adverse reactions were gastrointestinal in nature and mild to moderate in severity.

Overall, the most common treatment-related adverse reactions in adult patients receiving a single 2-g dose of Zmax were diarrhea/loose stools (12%), nausea (4%), abdominal pain (3%), headache (1%), and vomiting (1%). The incidence of treatment-related gastrointestinal adverse reactions was 17% for Zmax and 10% for pooled comparators. Treatment-related adverse reactions following Zmax treatment that occurred with a frequency of <1% included the following:

**Cardiovascular:** palpitations, chest pain

**Gastrointestinal:** constipation, dyspepsia, flatulence, gastritis, oral moniliasis

**Genitourinary:** vaginitis

**Nervous System:** dizziness, vertigo

**General:** asthenia

**Allergic:** rash, pruritus, urticaria

**Special Senses:** taste perversion

##### Laboratory Abnormalities

In subjects with normal baseline values, the following clinically significant laboratory abnormalities (irrespective of drug relationship) were reported in Zmax clinical trials:

- with an incidence of greater than or equal to 1%: reduced lymphocytes and increased eosinophils; reduced bicarbonate;

- with an incidence of less than 1%: leukopenia, neutropenia, elevated bilirubin, AST, ALT, BUN, creatinine, alterations in potassium.

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

##### Pediatric Patients:

The data described below reflect exposure to Zmax in 907 pediatric patients. The population was 3 months to 12 years of age. All patients received a single 60 mg/kg oral dose of Zmax. As in adults, the most common treatment-related adverse reactions in pediatric subjects were gastrointestinal in nature. The pediatric subjects all received a single 60 mg/kg dose (equivalent to 27 mg/lb) of Zmax.

In a study with 450 pediatric subjects (ages 3 months to 48 months), vomiting (11%), diarrhea (10%) loose stools (9%), and abdominal pain (2%) were the most frequently reported treatment-related gastrointestinal adverse reactions. Many treatment related gastrointestinal adverse reactions with an incidence greater than 1% began on the day of dosing in these subjects [43%(68/160)] and most [53%(84/160)] resolved within 48 hours of onset. Treatment-related adverse events that were not gastrointestinal, occurring with a frequency  $\geq$  1% were: rash (5%), anorexia (2%), fever (2%), and dermatitis (2%).

In a second study of 337 pediatric subjects, ages 2 years to 12 years, the most frequently reported treatment-related adverse reactions also included vomiting (14%), diarrhea (7%), loose stools (2%), nausea (4%) and abdominal pain (4%).

A third study investigated the tolerability of two different concentrations of azithromycin oral suspension in 120 pediatric subjects (ages 3 months to 48 months), all of whom were treated with azithromycin. The study evaluated the hypothesis that a more dilute, less viscous formulation (the recommended 27 mg/mL concentration of Zmax) is less likely to induce vomiting in young children than a more concentrated suspension used in other pediatric studies. The vomiting rate for subjects taking the dilute concentration azithromycin was 3% (2/61). The rate was numerically lower but not statistically different from the vomiting for the more concentrated suspension. Across both treatment arms, the only treatment-related adverse events with a frequency of  $\geq$ 1% were vomiting (6%, 7/120) and diarrhea (2%, 2/120).

Treatment-related adverse reactions with a frequency of <1% following Zmax treatment in all 907 pediatric subjects in the Phase 3 studies were:

**Body as a whole:** chills, fever, flu syndrome, headache;

**Digestive:** abnormal stools, constipation, dyspepsia, flatulence, gastritis, gastrointestinal disorder, hepatitis;

**Hemic and Lymphatic:** leukopenia;

**Nervous System:** agitation, emotional lability, hostility, hyperkinesia, insomnia, irritability, parosmia, somnolence;

**Respiratory:** asthma, bronchitis, cough increased, dyspnea, pharyngitis, rhinitis;

**Skin and Appendages:** dermatitis, fungal dermatitis, maculopapular rash, pruritus, urticaria;

**Special Senses:** otitis media, taste perversion;

**Urogenital:** dysuria.

##### Laboratory Abnormalities

In subjects with normal baseline values, the following clinically significant laboratory abnormalities (irrespective of drug relationship) were reported in Zmax pediatric clinical trials:

- with an incidence of greater than or equal to 1%: elevated eosinophils, BUN, and potassium; decreased lymphocytes; and alterations in neutrophils;

- with an incidence of less than 1%: elevated SGOT, SGPT and creatinine; decreased potassium; and alterations in sodium and glucose.

##### Postmarketing experience with other azithromycin products

Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

Adverse events reported with azithromycin immediate release formulations during the post-marketing period for which a causal relationship may not be established include:

**Allergic:** arthralgia, edema, urticaria and angioedema

**Cardiovascular:** palpitations and 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, acute renal failure, moniliasis and vaginitis

**Hematopoietic:** thrombocytopenia, mild neutropenia

**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, rash, photosensitivity, 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/smell perversion and/or loss

#### DRUG INTERACTIONS

##### Warfarin

Although, in a study of 22 healthy men, a 5-day course of azithromycin did not affect the prothrombin time from a subsequently administered dose of warfarin, spontaneous post-marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

##### USE IN SPECIFIC POPULATIONS

##### 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 daily doses in rats and mice, based on mg/m<sup>2</sup>, are estimated to be approximately equivalent to one or one-half of, respectively, the single adult oral dose of 2 g. 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.

##### Pediatric Use

Safety and effectiveness in the treatment of pediatric patients under 6 months of age have not been established.

**Community-Acquired Pneumonia:** The safety and effectiveness of Zmax have been established in pediatric patients 6 months of age or older with community-acquired pneumonia due to *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae* or *Streptococcus pneumoniae*. Use of Zmax for these patients is supported by evidence from adequate and well-controlled studies of Zmax in adults with additional safety and pharmacokinetic data in pediatric patients.

**Acute bacterial sinusitis:** Safety and effectiveness in the treatment of pediatric patients with acute bacterial sinusitis have not been established.

##### Geriatric Use

Data collected from the azithromycin capsule and tablet formulations indicate that a dosage adjustment does not appear to be necessary for older patients with normal renal function (for their age) and hepatic function receiving treatment with Zmax.

In clinical trials of Zmax, 17% of subjects were at least 65 years of age (214/1292) and 5% of subjects (59/1292) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

##### Renal Impairment

No dosage adjustment is recommended for patients with GFR >10 mL/min. Caution should be exercised when Zmax is administered to patients with GFR <10 mL/min, due to a higher incidence of gastrointestinal adverse events (8 of 19 subjects) observed in a limited number of subjects with GFR <10 mL/min.

##### Gender

The impact of gender on the pharmacokinetics of azithromycin has not been evaluated for Zmax. However, previous studies have demonstrated no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment of Zmax is recommended based on gender.

##### OVERDOSAGE

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

Please see full Prescribing Information for additional information about Zmax.

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**‘Our findings support using early menopause as a marker of increased cardiovascular disease risk.’**

DR. WELLONS

were Hispanic, and 13% were Chinese American.

The researchers defined early menopause as occurring before age 46, either naturally or surgically through removal of both ovaries, and they tracked the incidence of CVD among all study participants. This included heart attack, nonfatal cardiac arrest, a definite angina, probable angina (if followed by revascularization), a stroke, or death due to stroke, heart attack, or other cardiovascular disease.

At baseline, the women ranged in age from 45 to 84 years. Of the 2,509 women, 693 (28%) reported early menopause. Of these, 446 (64%) had natural menopause and 247 (36%) had surgical menopause.

In the early menopause group, 41 women (5.9%) had CVD events during the study period. Among those who did not have early menopause, 47 women (2.6%), had CVD events. The difference was significant.

No woman in either group had a CVD event before the age of 55.

After adjusting for race/ethnicity, level of education, smoking history, hypertension, total cholesterol, HDL cholesterol, diabetes, and whether the menopause was natural or surgical, Dr. Wellons and her associates found that women in the early menopause group were 2.1 times more likely to experience a CVD event, compared with women who did not have early menopause. Further adjustment for current or previous use of hormone replacement therapy and body mass index produced identical results.

Dr. Wellons was the recipient of an NHLBI Career Development Award. ■