

CLINICAL CAPSULES

Women Prefer Female Endoscopists

Nearly half of women prefer a female endoscopist for colorectal cancer screening, reported Stacy B. Menees, M.D., and her associates at the University of Michigan, Ann Arbor.

A questionnaire completed by 202 of 212 women while waiting for the primary care physician (PCP) showed that 43% preferred a woman endoscopist; 69% of these women had a female PCP.

Among women with a female preference, 87% were willing to wait more than 30 extra days for a woman and 14% would

be willing to pay more for a woman. Overall, 5% of the respondents would refuse to undergo a colonoscopy unless guaranteed a woman. In a multivariate logistic regression analysis, having a female PCP and being currently employed were independent predictors of preferring a female endoscopist (*Gastrointest. Endosc.* 2005;62:219-23).

Female Victimization and Violence

Girls who reported being the victims of violence were 2.2 times more likely to engage in violent behavior themselves, wrote

Beth E. Molnar, Sc.D., and her colleagues at the Harvard School of Public Health, Boston (*Arch. Pediatr. Adolesc. Med.* 2005;159:731-9).

In a longitudinal study, a population-based sample of 637 girls aged 9-15 years at baseline participated in three home interviews between November 1995 and January 2002.

Overall, 38% of the girls reported engaging in at least one violent act during the previous 12 months at baseline; 28% reported violent behavior during the past 12 months at the first follow-up interview; and 14% reported violent behavior at the second follow-up interview.

S. aureus Tied to Surgical Infection

Surgical site infections were significantly more likely among women who harbored *Staphylococcus aureus* prior to undergoing breast cancer surgery, according to data from 615 patients, A. Krishna, M.D., said at the joint annual meeting of the Surgical Infection Society and the Surgical Infection Society-Europe.

In a multicenter, prospective study conducted by Dr. Krishna and his colleagues at South Glasgow (Scotland) University Hospital, 83 of the 615 women (14%) carried *S. aureus*, as determined by preoperative nasal, axillary, and perineal swabs.

Within 30 days post surgery, surgical site infections occurred in 22 of the 83 women with *S. aureus*, compared with 75 of 532 women without *S. aureus* (27% vs. 14%, respectively).

The women enrolled in the study were undergoing primary surgery for breast cancer and were part of a larger randomized, controlled study of prophylactic antibiotic use.

Older Moms May Have Special Genes

Women who give birth after age 45 may have a special set of genes that makes them more fertile than average women, according to Israeli researchers.

"These women are models for us to learn about fertility," Neri Laufer, M.D., said at the annual meeting of the European Society of Human Reproduction and Embryology.

Dr. Laufer of Hadassah University Medical Center, Jerusalem, outlined his work with more than 200 Ashkenazi Jewish women who had conceived spontaneously after the age of 45 (*Fertil. Steril.* 2004;81:1328-32). "More than 80% of these women have six children or more and a low miscarriage rate," he said. Genetic profiling performed on eight of these women identified a clustering of genes that decreases apoptosis and increases DNA repair.

"These women appear to differ from the normal population due to a unique genetic predisposition that protects them from the DNA damage and cellular aging that helps age the ovary," Dr. Laufer said.

Discuss Wine With Pregnant Patients

Take time to focus specifically on wine consumption when routinely questioning pregnant patients about their use of alcohol.

That was the message in a poster on a study of alcohol consumption during pregnancy presented at the annual meeting of the Teratology Society.

The prospective, clinic-based cohort study involved 4,494 women interviewed at their first prenatal visit. Of these, 16% reported signs consistent with alcohol abuse and dependence, and half of those reported steady or binge drinking during pregnancy, reported William Rayburn, M.D., of the University of New Mexico, Albuquerque, and his colleagues.

In all, 208 of the women with signs of alcohol abuse or dependence completed the study.

Wine was the beverage of choice for about 25% of participants. Those who drank wine tended to consume lower quantities of alcohol, but a high percentage (43%) of wine drinkers continued their wine drinking after becoming aware of their pregnancy.

—From staff reports

Levofloxacin (levofloxacin) is a registered trademark of Ortho-McNeil Pharmaceutical Inc.

Reference: 1. Breen J, Chandra R, Herbig S, Lo J, Appel L. Zmax: a novel microsphere-based azithromycin dosage form. Poster for presentation at the American Association of Pharmaceutical Scientists: November 6-10, 2005; Nashville, Tenn.

Zmax™
(azithromycin extended release) for oral suspension
BRIEF SUMMARY

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 bacteria.

INDICATIONS AND USAGE

Zmax is indicated for the treatment of patients with mild-to-moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. (Please see **DOSE AND ADMINISTRATION** for specific dosing recommendations.)

Adults:

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.

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

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 using other formulations. 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 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.

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 excreted 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 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.

Information for Patients: Patients should be instructed to take Zmax on an empty stomach (at least 1 hour before or 2 hours following a meal).

The patient should be instructed to contact a physician immediately if any signs of an allergic reaction occur.

Patients who vomit within the first hour should contact their health care provider about further treatment.

Keep bottle tightly closed. Store at room temperature. Use within 12 hours of constitution. Shake bottle well before use. The entire contents of the bottle should be consumed.

Patients should be advised that Zmax may be taken without regard to antacids containing magnesium hydroxide and/or aluminum hydroxide.

Patients should be counseled that antibacterial drugs including Zmax should only be used to treat bacterial infections. They do not treat viral infections (eg, the common cold). Not taking the complete prescribed dose 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 Zmax or other antibacterial drugs in the future.

Drug Interactions: Co-administration of nelfinavir at steady-state with a single dose of azithromycin (2 x 600 mg tablets) results in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, 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 co-administered 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, they have been observed with macrolide products. Until further data are developed regarding drug interactions 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

Cyclosporine, hexobarbital, and phenytoin concentrations

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

Repeat Treatment: Studies evaluating the use of repeated courses of Zmax have not been conducted.

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 in rats given daily doses up to 10 mg/kg (approximately 0.05 times the single 2.0 g oral adult human dose on a mg/m² basis).

Pregnancy: Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (ie, 200 mg/kg/day). These daily doses in rats and mice, based on mg/m², are estimated to be approximately equivalent to one or one-half of, respectively, the single adult oral dose of 2.0 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.

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, 16.6% of subjects were at least 65 years of age (214/1292) and 4.6% 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.

Zmax 2.0 g oral suspension contains 148 mg of sodium.

ADVERSE REACTIONS

In controlled Phase 3 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 subjects receiving a single 2.0 g dose of Zmax were diarrhea/loose stools (11.6%), nausea (3.9%), abdominal pain (2.7%), headache (1.3%), and vomiting (1.1%). The incidence of treatment-related gastrointestinal adverse reactions was 17.2% for Zmax and 9.7% for pooled comparators.

No other treatment-related adverse events occurred in subjects on Zmax with a frequency of ≥1%. 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, loose stools. **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 ≥1%: reduced lymphocytes and increased eosinophils; reduced bicarbonate

—with an incidence of <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.

Post-Marketing Experience with Azithromycin Immediate Release

Adverse events reported with azithromycin 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 perversion.

DOSE AND ADMINISTRATION (See INDICATIONS AND USAGE.)

Zmax should be taken as a single 2.0 g dose. Zmax provides a full course of antibacterial therapy in a single oral dose. It is recommended that Zmax be taken on an empty stomach (at least 1 hour before or 2 hours following a meal).

In the Phase 3 program, no patient vomited within 5 minutes of dosing Zmax. In the event that a patient vomits within 5 minutes of administration, the health care provider should consider additional antibiotic treatment since there would be minimal absorption of azithromycin. Since insufficient data exist on absorption of azithromycin if a patient vomits between 5 and 60 minutes following administration, alternative therapy should be considered. Neither a second dose of Zmax nor alternative treatment is warranted if vomiting occurs ≥60 minutes following administration, in patients with normal gastric emptying.

Instructions for Pharmacist: Constitute with 60 mL of water and replace cap. Shake bottle well before dispensing.

Special Populations:

Renal Insufficiency: No dosage adjustment is recommended for patients with renal impairment (GFR 10-80 mL/min). Caution should be exercised when Zmax is administered to patients with end-stage renal disease (GFR <10 mL/min).

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

For more detailed professional information please refer to the full prescribing information.

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