

# Pipeline for Heart Failure Drugs Is Chock Full

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VANCOUVER, B.C. — The recent big therapeutic successes in heart failure have come from implantable electrophysiologic devices—cardiac resynchronization therapy, implantable cardioverter defibrillators—and surgical advances, such as ventricular reduction procedures.

Although attempts to develop new drugs have been disappointing lately, that

may be about to change, Robert E. Hobbs, M.D., said at a meeting sponsored by the International Academy of Cardiology.

Many heart failure drugs are wending through the developmental process. Each listed here has shown promise in clinical trials, and each addresses a different hypothesis about the nature of worsening heart failure; however, they constitute only a portion of what's in the pipeline, said Dr. Hobbs of the Cleveland Clinic Foundation.

► **A xanthine oxidase inhibitor.** Oxy-purinol, an analogue of allopurinol, inhibits xanthine oxidase, the enzyme that produces uric acid, as well as harmful oxygen free radicals. Xanthine oxidase is upregulated in heart failure. By inhibiting this enzyme, oxypurinol has been shown to improve myocardial energetics and endothelial function.

The Oxypurinol Therapy for Congestive Heart Failure (OPT-CHF) trial is a recently completed 400-patient phase II/III

randomized double-blind trial. The data are now being analyzed and are due to be presented this fall at the annual meeting of the American Heart Association.

► **A unique inotropic agent.** Levosimendan's mechanism of action differs from that of other inotropes, such as dobutamine and milrinone. It binds to cardiac troponin C. Levosimendan is categorized as a calcium-sensitizing agent because it enhances myocardial contractility without increasing intracellular calcium concentrations. The drug also acts as a vasodilator through activation of potassium channels. Moreover, it's a weak phosphodiesterase inhibitor as well.

Levosimendan's hemodynamic effects include an increase in cardiac index along with systemic and coronary vasodilation. In heart failure patients, levosimendan reduces elevated intracardiac pressures without increasing myocardial oxygen consumption. Unlike other inotropes, it has low arrhythmic potential, he stressed.

Levosimendan is approved for use in more than 30 countries as a treatment for patients with decompensated heart failure in need of inotropic support. But not in the United States.

An intravenous version of levosimendan is being studied today. The 800-patient phase-III Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE) trial is due to be presented in November at the AHA meeting.

► **A thyroid hormone analogue.** Roughly 30% of patients with advanced heart failure have low T<sub>3</sub> and normal TSH. Giving T<sub>3</sub> to patients with heart failure confers multiple cardiovascular benefits, including positive inotropic effects, improved diastolic relaxation, and stimulation of alpha-myosin heavy chain gene expression. But it also causes tachycardia, largely negating the improved cardiac performance.

Treatment with 3,5-diiodothyropropionic acid (DITPA), a T<sub>3</sub> analogue, offers similar cardiovascular benefits—but without the tachycardia. A 40-center, 34-week randomized trial is underway in 150 patients with class III/IV heart failure, low ejection fraction, low T<sub>3</sub>, and normal TSH. Participants are assigned to one of two doses of DITPA or placebo.

► **Adenosine receptor antagonists.** These agents cause afferent arteriolar dilatation. They promote diuresis while preserving renal function and maintaining glomerular filtration rate. One agent—known only as KW-3902—is the subject of an ongoing clinical trial in 200 hospitalized heart failure patients with impaired renal function. It's a 4-day treatment study with 30-day follow-up.

► **Vasopressin antagonists.** Nicknamed "super diuretics," these drugs cause profound diuresis without disrupting electrolytes. The target of these drugs (vasopressin) is synthesized by the hypothalamus in response to baroreceptor and osmotic stimuli. It causes vasoconstriction and sodium and water retention.

Two vasopressin antagonists, or "vaptans," have been tested in clinical trials: conivaptan and tolvaptan. Results are probably several years off, according to Dr. Hobbs. ■

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

**References:** 1. Anastasio GD, Little JM, Robinson MD, et al. Impact of compliance and side effects on the clinical outcome of patients treated with oral erythromycin. *Pharmacotherapy*. 1994;14:229-234. 2. 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 **DOSAGE 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/m<sup>2</sup> 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/m<sup>2</sup>, 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.

### DOSAGE 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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