DRUG FORMULARY REVIEW™
Utilization, Criteria and Outcomes

THOMSON
AMERICAN HEALTH CONSULTANTS™

IN THIS ISSUE

MARCH 2004
VOL. 20, NO. 3 • (pages 17-24)

New guidelines announced for preventing heart disease in women

Recommendations should help reduce 'gender gap'

The American Heart Association (AHA) in Dallas has released new guidelines for preventing heart disease and stroke in women that are tailored to each individual's cardiac event risk.

In the guidelines, women age 20 and older are treated based on whether they are high, intermediate, or low risk for having a heart attack in the next 10 years **(see explanation of risk on p. 18)**. "The concept of CVD [cardiovascular disease] as a categorical, 'have-or-have-not' condition has been replaced with a growing appreciation for the existence of a continuum of CVD risk," according to the AHA panel and writing group.

The guidelines, published in the Feb. 10 issue of the journal *Circulation*, call attention to the leading killer of women, reports **C. Noel Bairey Merz**, MD, medical director of the Preventive and Rehabilitative Cardiac Center at Cedars-Sinai Medical Center in Los Angeles and associate professor of clinical medicine for the Department of Medicine at the University of California, Los Angeles, School of Medicine. "There has been sufficient amount of new data that were specific to women that we could use to craft more specific recommendations."

The difference now is management, she says. "We've known about risk factors since Framingham [Heart Study], which was 50% women. We have always had good risk factor data. What's new is that we can manage the risk factors better and prevent more disease."

Treatment by risk category

The risk scheme allows health care providers to match the intensity of risk intervention to the baseline level of CVD risk. Here are some of the treatment recommendations for each risk category:

• **High risk.**

— Cholesterol-lowering therapy (preferably a statin) should be initiated simultaneously with lifestyle therapy in high-risk women, even if their LDL-C levels are below 100 mg/dL, unless contraindicated.

— Aspirin therapy (75-162 mg), or clopidogrel if patient is intolerant to aspirin, should be used in high-risk women unless contraindicated.

— Beta-blockers should be used indefinitely in all women who have had a myocardial infarction or who have chronic ischemic syndromes unless contraindicated.

— ACE (angiotensin-converting enzyme) inhibitors should be used in high-risk women, unless contraindicated. ARBs (angiotensin receptor blockers) should be used in high-risk women with clinical evidence of heart failure or an ejection fraction of less than 40% who are intolerant to ACE inhibitors.

— Women with CVD should be evaluated for depression and refer/treat when indicated.

— Omega-3 fatty-acid and folic acid diet supplementation may be considered.

• **Intermediate risk.**

— Cholesterol-lowering therapy (preferably a statin) should be initiated if LDL-C level is 130 mg/dL or greater on lifestyle therapy, or niacin or fibrate therapy when HDL-C is low or non-HDL-C elevated after LDL-C goal is reached.

— Aspirin therapy (75-162 mg) should be considered in intermediate-risk women as long as blood pressure is controlled and the benefit is likely to outweigh risk of gastrointestinal side effects.

• **Lower risk.**

— Cholesterol-lowering therapy should be considered in low-risk women with 0 or 1 risk factor when LDL-C level is 190 mg/dL or greater, or if multiple risk factors are present when LDL-C is 160 mg/dL or greater, or niacin or fibrate therapy when HDL-C is low or non-HDL-C elevated after LDL-C goal is reached.

— Routine use of aspirin in lower-risk women is not recommended pending the results of ongoing trials.

Other notable recommendations

The guidelines also recommended:

— Pharmacotherapy is indicated when blood

CVD risk for women explained

The American Heart Association guidelines categorize women age 20 and older by their risk of cardiovascular disease (CVD). The risk groups are defined by their absolute probability of having a coronary event in 10 years, according to a scoring method developed by the Framingham Heart Study, which began in 1948 and was sponsored by the National Heart, Lung, and Blood Institute. The risk groups include:

• **High risk**. These are women with a greater than 20% risk of having a coronary event in 10 years. Some clinical examples include established CHD, diabetes, and chronic kidney disease.

• **Intermediate risk**. These women have a 10%-20% risk of having a coronary event in 10 years. Some clinical examples include multiple risk factors and first-degree relative(s) with early onset atherosclerotic CVD.

• **Lower risk.** These women have less than 10% risk of having a coronary event in 10 years. This may include women with one or no risk factors. ■

Drug Formulary Review (ISSN#1548-2790), including **Drug Criteria & Outcomes**™, is published monthly by Thomson American Health Consultants, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodical postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **Drug Formulary Review**, P.O. Box 740059, Atlanta, GA 30374.

Subscriber Information

Customer Service: (800) 688-2421 or fax (800) 284-3291, (customerservice@ahcpub.com) **Hours of operation:** 8:30 a.m.-6 p.m. Monday-Thursday; 8:30 a.m.-4:30 p.m. Friday.

Subscription rates: One year (12 issues), $479. Outside U.S., add $30 per year, total prepaid in U.S. funds. Two to nine additional copies, $383 per year; 10 to 20 additional copies, $287 per year. For more than 20 copies, contact customer service at (800) 688-2421. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue date. **Back issues**, when available, are $80 each. (GST registration number R128870672.)

Editorial Questions

Questions or comments? Call **Lee Landenberger** at (404) 262-5483.

Editor: **Sue P. Coons**, (spcoons@aol.com).
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@thomson.com).
Editorial Group Head: **Lee Landenberger**, (404) 262-5483, (lee.landenberger@thomson.com).
Managing Editor: **Paula Cousins**, (816) 960-3730, (paula.cousins@thomson.com).
Production Editor: **Nancy McCreary**.

pressure is 140/90 mm Hg or greater. The blood pressure can even be lower in the setting of blood pressure-related target-organ damage or diabetes. Thiazide diuretics should be part of the drug regimen for most patients unless contraindicated.

— Among women with chronic or paroxysmal atrial fibrillation, warfarin should be used to maintain the INR (international normalized ratio) at 2.0-3.0 unless the women are considered to be at low risk for stroke or high risk of bleeding. Aspirin (325 mg) should be used in women with chronic or paroxysmal atrial fibrillation with a contraindication to warfarin or at low risk for stroke.

— Hormone therapy and antioxidant supplements should not be used to prevent CVD.

Bairey Merz hopes these recommendations will reduce the treatment gender gap between men and women. "Ace inhibitors and beta-blockers were previously recommended, but high-risk women are anywhere from 5% to 20% less likely to be prescribed these pills."

High-risk women should be identified and treated, she continues. "We should not be faced with these gender gaps the next time we look five to 10 years down the line." ■

Cost-effectiveness analysis gives global view of price

Results expand direct cost analysis

While on rotation as a drug information specialty resident, one pharmacist decided to take a more comprehensive look at how much one drug would cost the health center if it were added to the formulary.

Enoxaparin was the first-line agent being used at the University of Pittsburgh Medical Center as treatment for venous thromboembolism (VTE) prophylaxis in orthopedic hip surgery patients. "We looked at adding fondaparinux as an alternative first-line agent based on efficacy, but we wanted to present the Pharmacy and Therapeutics Committee with a more broad analysis of cost. Looking at the agents on straight acquisition cost only, did not support our recommendation to add the agent as a first-line alternative to enoxaparin," reports **Bethany A. Fedutes**, PharmD, drug information specialty resident.

She and other researchers decided to implement a model cost-effectiveness analysis (CEA) of the drug, to look at overall cost consequences. "I wouldn't say that the cost-effectiveness analysis is better than looking at the cost itself, but it is more informative for the overall health system," she says.

Fedutes developed the analysis through a literature search, implementation of a decision tree analysis, and the use of triage data software.

"When looking at any pharmaco-economic analysis, there are steps and procedures of collecting data on event rate, efficacy, and costs." In addition, prior cost-effective analysis may be available in which you can possibly input your data or pull medication costs or direct and indirect medical costs from the primary literature, she says.

Comparing the two analyses

Once the analysis was complete, Fedutes compared the results to enoxaparin use, looking at factors such as average cost and probability of death avoided. The picture was definitely different than looking at straight drug cost, she says. Although fondaparinux is a more expensive agent, the cost/effectiveness (cost/probability of death avoided) incremental difference between the two agents was $149.33.

"When you factor in effect and other indirect or direct medical costs, there was more of a cost neutralization that was seen after the analysis was performed than specifically looking at straight acquisition costs of the agent," Fedutes explains.

The details from the CEA helped shape the formulary decision process. "It gives a more global picture of the effect of the drug on the formulary or on the costs of the health system," Fedutes says. The Pharmacy and Therapeutics Committee made the recommendation to add fondaparinux as a first-line low molecular weight heparin agent for VTE prophylaxis in hip fracture patients.

[***Editor's note:*** *The results of this analysis were presented during the Drug Information Innovations Session at the December clinical meeting of the American Society of Health-System Pharmacists in New Orleans. Other researchers involved in the project were Nicole T. Ansani, PharmD, associate director of the Drug Information Center at the University of Pittsburgh School of Pharmacy; and Susan J. Skledar, RPh, MPH, director of Drug Use & Disease State Management at the University of Pittsburgh Medical Center.*]

Pilot program offers one-on-one consultations

Program to improve care and save money

By calling an 800 number and paying a $5 fee, residents in four Wyoming cities can have face-to-face consultations with clinical pharmacists, who not only review the residents' health and medication history but make cost-saving suggestions as well.

"With the rising cost of medications and with so many people — especially seniors — having to pay for them on their own, it is a real benefit to have a pharmacist consultation that takes a professional look at their medications and sees if there are perhaps some alternative choices," says **Aimee Lewis**, PharmD, pharmacist consultant with the Wyoming Department of Health.

To become part of the program, residents in Casper, Cheyenne, Laramie, and Torrington first call the Wyoming Pharmacist 800 number. The number is being marketed through flyers and some newspaper ads sponsored by AARP Wyoming. The Department of Health has emphasized that this is not an information hotline. "A pharmacist does not answer the phone," she says. "Instead, the 800 number focuses on getting residents one-on-one consultations in their area."

The Department of Health has contracted with the University of Wyoming School of Pharmacy in Laramie to man the call center and provide consulting services. When a resident calls the number, a receptionist takes basic information and sends the resident a form packet. The resident fills out the form and sends it to the Department of Health.

The form asks for demographic information to help with statistical tracking of the program, Lewis notes. The resident also is asked to list every medication he or she is taking, including over-the-counter and herbal medications. In addition, the resident is asked to list physician and insurance information. "We might be able to look at their [health plan] formularies and make appropriate changes for the residents," she adds.

Once the Department of Health receives the form and the resident's $5 consultation fee, the resident is assigned a clinical faculty member from the school of pharmacy who is under contract with the program. "Once the consultant pharmacist gets the information, we ask that he or she contacts the person within two weeks to set up a time to meet," Lewis says.

At this point the Department of Health does not use specific guidelines as to how the pharmacists conduct the consultation. "These pharmacists generally work in hospitals or family practice-type settings so [this kind of consultation] is something they generally do on a daily basis," she says. The pharmacists receive $70 for each consultation.

If the program expands or goes statewide, however, the department may offer a continuing education (CE) or some other training program for pharmacists who are interested. The pharmacists would contract with the program directly through the department. The CE or training program probably would provide a format for the consultation to make it more systematic, Lewis reports.

The process for the pilot program began when Ralph Bartholomew, RPh, spoke to the Wyoming legislature about a similar project he had set up at a company in Worland, WY. "He spoke about how he was saving his clients some money on their prescription drug bills," Lewis recalls. Bartholomew's successful lobbying helped get the legislation passed last session, and partial funding became available July 1, 2003. The Department of Health immediately began working on setting up the pilot program, which was implemented Dec. 4.

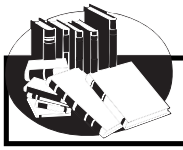
As of Jan. 2 — the first month of operation — the hotline has received 80 calls, which have resulted in 97 packets of information being mailed, she reports. About 50 forms have been returned and sent out for consultations.

The pilot program offers a great service to the residents of the four cities, according to Lewis. Residents may have multiple prescribers who may or may not be aware of all the drugs the residents are taking.

The pharmacists can look at the residents' overall drug regimen to make sure none of the drugs have adverse effects or negatively react with each other. The pharmacists also can make suggestions about alternative medications that may save the residents money.

For example, if they take prescription Prilosec and they can take the over-the-counter version instead, it could save them from $40 to $60 a month depending on the strength and how much they are taking, Lewis says.

After the consultation, the pharmacists make recommendations that are sent to the residents as well as to their prescribers, who should approve any changes to the residents' medications. "I think the consultations will not only save money but will result in better care for the patient," she says. ■



JOURNAL REVIEW

Memantine shows benefit for moderate-to-severe AD

New approach warrants further research

Memantine (Namenda) helped lessen the symptoms of patients with moderate-to-severe Alzheimer's disease (AD) who were already receiving treatment with donepezil (Aricept), according to a study published in the Jan. 21 issue of the *Journal of the American Medical Association.*

Memantine is a low- to moderate-affinity, uncompetitive N-methyl-D-aspartate receptor antagonist. The U.S. Food and Drug Administration approved it October 2003 for the treatment of moderate-to-severe AD. Researchers decided to study it in patients who were already receiving a cholin-esterase inhibitor. Forest Laboratories, which markets memantine, provided financial and material support for the research.

About 400 participants with moderate-to-severe AD and Mini-Mental State Examination scores of 5-14 began the randomized, double-blind trial, which was conducted at 37 U.S. sites between June 11, 2001, and June 3, 2002. The participants must have received ongoing cholinesterase inhibitor therapy with donepezil for more than six months before the trial and be at a stable dose (5-10 mg/d) for at least three months.

When the trial began, the participants were randomized to receive memantine (starting dose 5 mg/d, increased to 20 mg/d) or placebo for 24 weeks. Participants not tolerating the target dose by week 8 were removed from the trial. A total of 322 patients completed the study. Significantly more participants in the memantine group (85% as compared to 75% in the placebo group) completed the study.

The researchers found that measures of cognitive function, activities of daily living, behavior, and clinical global status were significantly improved with memantine compared with placebo. The drug seemed to be well tolerated, too. Significantly more patients in the placebo group discontinued the trial than in the memantine group. In addition, fewer participants in the memantine group discontinued the trial due to adverse events.

The primary adverse effect attributed to memantine use was confusion, which occurred at a median of 32 days. The confusion, however, was usually mild and did not last long. Some participants also complained of headache, but this seldom lasted more than one day. Gastrointestinal adverse effects, such as diarrhea and fecal incontinence, were reported more in the placebo group.

The researchers concluded from their study that memantine "represents a new approach for the treatment of patients with moderate-to-severe AD." However, the researchers say there are limitations to their results. First, the trial did not address different doses or titration rates, the use of other cholinesterase inhibitors besides donepezil, or the impact of beginning memantine therapy before donepezil.

In addition, the trial does not address the long-term effects of memantine and cholinesterase inhibitor treatment. The researchers say that this will be the focus of an open-label extension and other ongoing trials. ■

NEWS BRIEFS

New hepatotoxicity warning added to nevirapine (Viramune)

Boehringer Ingelheim Pharmaceuticals is informing health care professionals about new labeling information being added to the boxed warning for nevirapine (Viramune), a non-nucleoside reverse transcriptase inhibitor indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Specifically, the company gives these warnings:

- Women with CD4+ counts greater than 250 cells/mm^3, including pregnant women receiving chronic treatment for HIV infection, are at considerably higher risk (twelvefold) of hepatotoxicity. Some of these events have been fatal. This subset of patients was identified by analyses of CD4 count at the time of initiation of nevirapine therapy.
- The greatest risk of severe and potentially fatal hepatic events (often associated with rash) occurs in the first six weeks of nevirapine treatment. However, the risk continues after this time and patients should be monitored closely for the first 18 weeks of treatment with nevirapine.

• In some cases, hepatic injury progresses despite discontinuation of treatment.

This new information is the result of recent post-marketing surveillance data and further analysis of the nevirapine clinical trial database.

The company reports that some experts recommend clinical and laboratory monitoring more often than once a month. They would include monitoring of liver function tests at baseline, at the time of dose escalation, and two weeks after dose escalation. All patients developing a rash, at any time during nevirapine treatment, but particularly during the first 18 weeks, should have liver function tests performed at that time. After the initial 18-week period, frequent clinical and laboratory monitoring should continue throughout nevirapine treatment. ▼

FDA announces improved drug approval results in 2003

The U.S. Food and Drug Administration announced improved results over last year on overall drugs and biologics approvals for calendar year 2003, and decreases in the time it took the agency to review and approve most applications.

The agency's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) approved 466 new and generic drugs and biological products.

In 2003 CDER approved 72 new drug applications (NDAs), compared with 78 in 2002 and 66 in 2001. Of these NDA approvals, 21 were New Molecular Entities (NMEs), with active ingredients never before marketed in the United States. This is up from the calendar year 2002 total of 17. Priority approvals — approvals for priority products of special medical importance — increased to 14 priority NDAs and nine priority NMEs in 2003, compared to 11 and seven, respectively, in 2002.

Median total approval time for CDER's priority NDAs was 7.7 months, compared with 19.1 months for 2002. FDA has attributed the 2002 figure to the effect of a few applications with unusually long regulatory histories. The median total approval time for standard NDAs was 15.4 months, also in line with the previous year (15.3 months).

For more details about 2003 CDER and CBER approvals, see www.fda.gov/bbs/topics/NEWS/2004/NEW01005.html. ▼

Savings noted with increased use of beta-blockers

Using a decision model, researchers estimate that Medicare costs would decrease if the use of beta-blocker drugs were more widespread, according to a new study sponsored by the Agency for Healthcare Research and Quality (AHRQ). The study, "Economic Effects of Beta-Blocker Therapy in Patients with Heart Failure," is published in the January issue of *American Journal of Medicine.*

Researchers from the AHRQ-sponsored Duke Center for Education and Research on Therapeutics in Durham, NC, estimated that treatment for heart failure without beta-blocker drugs would cost Medicare an estimated $39,739 per-patient over a five-year period; however, treatment with beta-blockers would cost an estimated $33,675 — a per-patient savings of $6,064. In contrast, beta-blocker therapy would increase expenses to Medicare patients by an estimated $2,113 over five years.

Although at the time of the study, Medicare did not cover prescription drugs, researchers estimated that program savings would remain positive even if Medicare reimbursed patients for the cost of beta-blockers.

Estimates in the study were calculated using a Markov decision model. Calculations were based on clinical trial data on rates of hospitalization/death and effectiveness of beta-blockers, Duke University Medical Center estimates of hospital costs and reimbursement, and physician fees from the Medicare fee schedule. ▼

First TB vaccine trial in 60 years to begin

A new vaccine, made with several proteins from the bacterium that causes tuberculosis (TB), will soon enter the first phase of human safety testing. The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, has supported research on the candidate vaccine from its earliest stages.

Corixa and GlaxoSmithKline Biologicals will conduct the trial in the United States. The vaccine combines two TB proteins known to stimulate strong immune responses in humans. The proteins initially were identified by screening blood taken from volunteers who never became ill with TB

despite long-term infection with *M. tuberculosis* bacteria. Using recombinant DNA technology, the TB proteins were fused and then combined with adjuvants. NIAID grants awarded in the late 1990s supported research that uncovered the most effective adjuvant-protein combination. ▼

Study: Consumers don't understand drug formularies

Many Americans do not understand one of managed care's most basic and universal tools to control prescription drug costs, according to a recent study.

The study, published in the January issue of *Managed Care Interface*, explained that the general public does not know the answers to most prescription drug questions such as "Why does one medication have a higher copayment at the pharmacy than another?" "Why are some drugs so much more expensive than others?" and "What is a formulary?" The authors believe that this lack of knowledge fuels health plan member dissatisfaction and frustration.

In the article, "Consumer Knowledge and Perceptions of Formularies" Sangit Sansgiry, PhD, and his team from the University of Houston College of Pharmacy noted that only 25% of 714 Houston health plan members responding to a survey had a copy of their drug formulary.

Once formularies were explained to members, the most prevalent attitude toward them was negative: 73% of the consumers believed that formularies compromised the quality of their medications; and 72% believed that the use of formularies encouraged the use of less effective medications. In addition, only 30% of the survey respondents were aware of the kind of information that was in their formulary.

One interesting finding in the study is that consumers generally were happy with their health plans, yet had negative attitudes toward formularies. The implementation of effective and consistent educational initiatives may be the answer to informing consumers about formularies and their role in the health care continuum. ▼

Vantin antibiotic batch recalled

Graham Development, a distributor in Oneonta, NY, has begun a voluntary recall of one lot of Vantin 200 mg tablets (Lot #K08210301), a prescription antibiotic. There is a possibility that product dispensed from this lot may contain the heart medication digoxin (Lanoxin). Consumers who inadvertently take digoxin while assuming it is Vantin are at risk of serious health consequences such as ventricular arrhythmia and death. Affected drug distributors and pharmacies are being notified.

The bottles in question may identify Graham Development or Pharmacia & Upjohn Co. as the source of the product and were dispensed after Dec. 12, 2003. Vantin tablets and digoxin tablets are different in color, size, shape, and markings. Vantin tablets are football shaped, orange/red, film-coated, and embossed with "U" and "3618," and Lanoxin tablets are round, white tablets, scored, and embossed "LANOXIN" and "X3A."

The approximately 420 bottles in distribution were shipped to pharmacies and distributors in the northeastern United States, Kentucky, Minnesota, Missouri, and South Dakota. ■

IN THE PIPELINE

• Myogen has begun patient enrollment in Phase III clinical trials of ambrisentan for the treatment of **pulmonary arterial hypertension**.

• Genome Sciences has begun dosing patients in a Phase II clinical trial of human monoclonal antibody to B-lymphocyte stimulator, BlyS (LymphoStat-B), for the treatment of **rheumatoid arthritis**.

• Favrille has completed enrollment for its

COMING IN FUTURE MONTHS

- Systematic approach to evaluating drotrecogin alfa (activated)
- A competency assessment tool for drug use policy and drug information
- Multitasking in pharmacy practice
- Aprepitant (Emend) formulary evaluation
- Rosevastatin (Crestor) drug evaluation

current Phase II clinical trial (FavId-04) with the company's lead investigational agent, FavId. This agent is under clinical development for the treatment of **follicular B-cell lymphomas following cytoreductive therapy with Rituxan**.

• Cytheris has announced the entry of its first recombinant human Interleukin-7 protein in a Phase I clinical study. This cytokine targets the **immune reconstitution of immunocompromised patients**, including those undergoing cancer treatment, affected by AIDS, or recovering from a bone marrow transplant.

• Coley Pharmaceutical Group has initiated a Phase I clinical study of CPG 10101 (Actilon), a novel synthetic TLR9 agonist, targeted for patients with **chronic hepatitis C infection**.

• Peninsula Pharmaceuticals has announced that patient enrollment has begun in a Phase I trial of an inhaled formulation of its lead product candidate, doripenem, a **broad-spectrum carbapenem antibiotic**.

• Epimmune has completed patient enrollment in the Phase I/II therapeutic **HIV vaccine** trial of its EP HIV-1090 vaccine candidate.

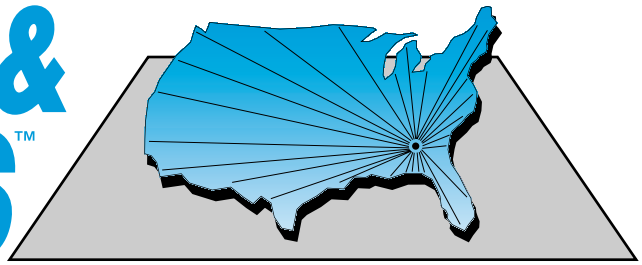
• Progen Industries Limited has begun a new Phase II clinical study of its lead **anticancer compound**, PI-88.

• Pharmacyclics has initiated a Phase I clinical trial evaluating the safety and efficacy of its investigational drug motexafin gadolinium (Xcytrin) in combination with temozolomide (Temodar) for the treatment of patients with **relapsed malignant gliomas**.

• Allos Therapeutics has initiated a Phase I clinical trial of efaproxiral (RSR13) and supplemental oxygen with concurrent chemoradiation therapy in patients with **locally advanced, unresectable (Stage IIIA/Stage IIIB) non-small cell lung cancer**.

• Genencor International is beginning Phase I safety and immunogenicity testing for its DNA-based therapeutic vaccine to treat **hepatitis B**. ■

DRUG CRITERIA & OUTCOMES™



Palonosetron (Aloxi) Formulary Evaluation

Part 1 of 2: Mechanism of Action, Pharmacokinetics, Indications, Dosage, and Administration

By **Brian Watkins**, PharmD Candidate
Harrison School of Pharmacy
Auburn (AL) University

Palonosetron, developed by MGI Pharma and its partner Helsinn Healthcare SA, is a recently approved selective antagonist of serotonin subtype 3 receptors (5-HT3).

Palonosetron's affinity for 5-HT3 receptors gives it utility as an antiemetic and antinauseant. Other "setrons" include ondansetron (Zofran), granisetron (Kytril), and dolasetron (Anzemet).

Mechanism of action

Palonosetron, as well as other setrons, inhibits emesis by blocking serotonin receptors both peripherally on vagal afferents and centrally in the chemoreceptor trigger zone (CTZ) of the area postrema.

Pharmacokinetics

***Absorption*:** Limited studies have demonstrated that following intravenous (IV) dosing, maximal plasma concentrations and area under the concentration-time curve are dose-proportional over the dose range of 0.3-90 ug/kg.

***Distribution*:** Palonosetron is 62% bound to plasma proteins and has a large volume of distribution equal to 8.3 +/- 2.5 L/kg.

***Metabolism*:** Fifty percent of the palonosetron dose is metabolized via the CYP450 system. In vitro studies implicate CYP2D6 to be the primary enzyme involved in palonosetron's metabolism; however, CYP3A and CYP1A2 may play minor roles. The major metabolites produced are N-oxide-palonosetron and 6-S-hydroxy-palonosetron, each

Table 1: Selected pharmacokinetic differences between available setrons

Parameter	Palonosetron	Ondansetron	Granisetron	Dolasetron
Bioavailability	IV = complete	PO (oral) = 56% IV = complete	PO = Not available IV = complete	PO = 75% IV = complete
Protein binding	62%	70%	65%	69-77%
Distribution	8.3 +/- 2.5 L/kg	Not available	Vd = 2-3 L/kg	5.8 L/kg
Metabolism	Substrate for CYP2D6	Extensive; CP3A4, CYP1A2, and CYP2D6	Substrate for CYP3A4	Hepatic; reduction (rapid)
Half-life (hours)	40 h	4 h	8.9 h	7.5 h
Elimination	Urine (40% as unchanged drug and 40% as metabolites)	Feces, < 10% unchanged in urine	Feces (34% as metabolites) and urine (12% unchanged drug and 34% as metabolites)	Urine as metabolite

Table 2: FDA-labeled indications for other currently available setrons

Ondansetron	• Prevention of nausea and vomiting associated with initial and repeat courses of moderately or highly emetogenic chemotherapy.
	• Prevention of nausea and vomiting associated with radiation therapy (total body and fractionated abdominal).
	• Prevention and treatment of postoperative nausea and vomiting (PONV).
Granisetron	• Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy.
	• Prevention of nausea and vomiting associated with radiation therapy (total body and fractionated abdominal).
Dolasetron	• Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy.
	• Prevention and treatment of PONV.

of which are virtually devoid of activity.

***Elimination*:** After a single intravenous carbon-14 labeled dose of palonosetron (10 ug/kg), approximately 80% of the dose was recovered within 144 hours in the urine. Approximately 40% of that dose is recovered as parent drug. Total body clearance of palonosetron is 160 +/- 35 mL/hr/kg and renal clearance was 66.5 +/- 18.2 mL/hr/kg.

The mean terminal elimination half-life is approximately 40 hours.

Kinetically, the major difference between palonosetron and other setrons is a mean terminal elimination half-life equal to 40 hours **(see Table 1)**. Another major difference that exists between the setrons is their relative selectivity for different isoenzymes of the CYP450 system.

Ondansetron and granisetron are both substrates for CYP3A4, the isoenzyme responsible for the metabolism of approximately 50% of marketed drugs.

Finally, ondansetron is eliminated primarily in feces while granisetron displays a more balanced elimination profile. Palonosetron and dolasetron are eliminated primarily in urine. Only small differences exist between the available agents with respect to bioavailability, protein binding, and distribution.

FDA-labeled indications

FDA-approved indications for palonosetron includes **(see Table 2 for other setrons)**:

• Prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy; and

• Prevention of delayed nausea and vomiting

Table 3: Comparison of dose vs. indication of other currently available setrons*

Indication	Palonosetron	Ondansetron	Granisetron	Dolasetron
CINV	IV = 0.25 mg as a single dose.[1, 2] Repeat dosing within seven days has not been evaluated.	IV = single 32 mg dose or three 15 mg/kg injections. PO = 24 mg[1] or 8 mg q8h x 2, then 8 mg q12h x 1-2d.[2]	IV = single 10 mcg/kg dose (repeat doses are anecdotal). PO = 2 mg q day or 1 mg bid.	IV = single 0.6-5 mg/kg dose or 50 mg bolus or 2.4-3 mg/kg infusion. PO = single 200 mg dose.
PONV	N/A	IM (intramuscular)/ IV = single 4 mg dose. PO = single 16 mg dose.	IV = single 1mg dose.	IV = 12.5 mg dose. PO = 100 mg dose (oral only for prevention, not treatment).
Radiation	N/A	PO = 8 mg[3] or 8 mg dose followed by 8 mg q8h.[4]	PO = 2 mg q day.	N/A

*Doses for adults

1 = highly emetogenic chemotherapy; 2 = moderately emetogenic chemotherapy; 3 = total body irradiation; 4 = fractionated abdominal irradiation.

Table 4: Comparison of administration vs. indication of other currently available setrons

Indication	Ondansetron	Granisetron	Dolasetron
CINV	IV = IVPB over 15 minutes (diluted) or IVP over 2-5 minutes ~ 30 minutes prior to chemotherapy. PO = first dose 30 minutes prior to chemotherapy.	IV = IVPB over 5 minutes ~ 30 minutes prior to chemotherapy. PO = One hour prior to initiation of chemotherapy.	IV = IVP over 30 seconds (undiluted) or IVPB over 15 minutes ~ 30 minutes prior to chemotherapy. PO = 1 hour prior to chemotherapy.
PONV	IV = 30 minutes before anesthesia discontinued or as treatment if vomiting occurs after surgery. PO = One hour prior to induction of anesthesia.	IV = IVP over 30 seconds (undiluted).	IV = 15 minutes before anesthesia discontinued. PO = 2 hours prior to surgery. (For treatment IV/PO = as soon as needed.)
Radiation	PO = 1-2 hours prior to initiation of radiotherapy.	PO = 1 hour prior to initiation of radiation.	N/A

IVPB = intravenous piggyback; IVP = intravenous pyelogram.

associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

Dosage and administration

The recommended dosage of palonosetron is 0.25 mg administered as a single dose approximately 30 minutes prior to the start of chemotherapy **(see Table 3)**. Any repeat dosing within seven days has not been evaluated and thus cannot be recommended. No dose adjustments are recommended for renal or hepatic impairment.

Palonosetron is administered intravenously over 30 seconds **(see Table 4)**. Palonosetron should not be mixed with other drugs; therefore, the infusion line should be flushed before and after with normal saline.

Clinical trials

To date, four clinical trials have evaluated the safety and efficacy of palonosetron in preventing acute and delayed chemotherapy-induced nausea and vomiting (CINV); however, only one of the four clinical trials has been published. Two Phase III trials compared single, fixed intravenous doses of palonosetron with either single-dose intravenous ondansetron or dolasetron for the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy.

Also, one Phase II dose-ranging study and a randomized, controlled Phase III trial have been conducted to evaluate palonosetron's safety and efficacy in preventing nausea and vomiting induced by highly emetogenic chemotherapy.

A discussion of clinical trial data, adverse effects, and cost analysis will appear in the April issue of *Drug Formulary Review's Drug Criteria & Outcomes.* ■

New FDA Approvals

These drugs recently received final approval from the U.S. Food and Drug Administration (FDA):

• ***New administration of peginterferon alfa-2a (Pegasys) by Roche.*** The FDA has approved prefilled syringes of peginterferon alfa-2a (Pegasys) for the treatment of chronic hepatitis C.

Peginterferon alfa-2a, a pegylated alpha interferon, and ribavirin (Copegus) were approved by the FDA in December 2002 for use in combination for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not previously been treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis.

Pre-filled syringes will be packaged four per box. Pegasys currently is available in vials as a pre-mixed solution.

Pegasys is dosed at 180 mcg as a subcutaneous injection taken once a week. Copegus is available as a 200 mg tablet, and is administered orally two times a day as a split dose.

• ***New indication for oxaliplatin for injection (Eloxatin) by Sanofi-Synthelabo.*** The FDA has approved oxaliplatin for injection (Eloxatin) in combination with 5FU/LV for the first-line treatment of advanced colorectal cancer. Oxaliplatin was approved in August 2002 for second-line treatment of patients with metastatic carcinoma of the colon or rectum in the United States.

Clinical data show that patients with advanced colorectal cancer treated with oxaliplatin given in combination with 5-FU/LV as first-line chemotherapy had a statistically significant improvement of nearly five months in median survival time compared to patients treated with a standard treatment of irinotecan in combination with 5-FU/LV.

• ***New dosing strategy for saquinavir mesylate 1,000 mg (Invirase) by Roche.*** The FDA has approved protease inhibitor saquinavir mesylate 1,000 mg (Invirase) for use with ritonavir (100 mg) in combination regimens for the treatment of HIV infection. This new dosing strategy increases blood levels of saquinavir to enable twice-daily dosing and eliminates the inadequate drug levels associated with use of saquinavir mesylate alone.

The FDA-approved dosing is 1,000 mg of saquinavir mesylate (5 x 200 mg capsules) in combination with ritonavir 100 mg, twice a day. Ritonavir should be taken at the same time as saquinavir mesylate. Saquinavir mesylate and ritonavir should be taken within two hours after a meal.

Coadministration of saquinavir and ritonavir has led to severe adverse events, mainly diabetic ketoacidosis and liver disorders, especially in patients with pre-existing liver disease. Therefore, saquinavir mesylate, when administered with ritonavir, is contraindicated in patients with severe hepatic impairment.

• ***Amlodipine besylate/atorvastatin calcium (Caduet) by Pfizer.*** The FDA has approved the dual-therapy medicine amlodipine besylate/atorvastatin calcium (Caduet) for the simultaneous treatment of high blood pressure and high cholesterol.

Caduet is the first medicine to treat two different conditions — high blood pressure and high cholesterol — in one pill. It contains both amlodipine besylate (Norvasc) for the treatment of high blood pressure and atorvastatin calcium (Lipitor) for high cholesterol.

Amlodipine besylate/atorvastatin calcium was well tolerated by patients in clinical trials and has been administered with a variety of antihypertensive medications, including thiazide diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors. The most common side effects reported by amlodipine besylate/atorvastatin calcium patients were fluid retention, headache, dizziness, abdominal pain, and weakness, and were characterized as mild to moderate.

The dual-therapy drug is contraindicated in patients with hypersensitivity to any component of this medication; in patients with active liver disease or unexplained persistent elevations of serum transaminases; and in nursing or pregnant women. With any statin, promptly report muscle pain, tenderness, or weakness, as it could be a sign of serious side effects. ■