DRUG FORMULARY REVIEW™
Utilization, Criteria and Outcomes

THOMSON™
AMERICAN HEALTH CONSULTANTS

IN THIS ISSUE

MAY 2004
VOL. 20, NO. 5 • (pages 33-40)

Statin research calls current guidelines into question

LDL-C levels may need to be lower than 100 mg/dL

New research is challenging the current guidelines of how to treat atherosclerotic coronary disease with statin drugs. Current guidelines by the National Cholesterol Education Program have set a therapy target of 100 mg/dL.

Two recent head-to-head trials, however, suggest that intensive statin therapy may be of greater benefit.

"The implications of this turning point — that is, of the new era of intensive statin therapy — are profound," says **Eric J. Topol**, MD, chairman and professor at the Department of Cardiology of The Cleveland Clinic Foundation. Topol's comments appeared in an editorial in the April 8 issue of the *New England Journal of Medicine*.

One of the trials, Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL), compared the effects of patients randomly assigned a moderate lipid-lowering regimen consisting of 40 mg pravastatin or an intensive lipid-lowering regimen consisting of 80 mg atorvastatin.

Between June 1999 and September 2001, 654 patients were randomized and received the study drug; 502 had intravascular ultrasound examinations to evaluate build-up in coronary arteries at baseline and after 18 months of treatment.

Baseline LDL-C level was reduced to 110 mg/dL in the pravastatin group and to 79 mg/dL in the atorvastatin group. In addition, progression of coronary atherosclerosis occurred in the pravastatin group (2.7%) compared with baseline. Progression did not occur in the atorvastatin group (-0.4%) compared with baseline. Both drugs showed a similar incidence of side effects.

"For patients with coronary heart disease, intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis compared with pravastatin," the researchers concluded. The study was funded by Pfizer, which makes atorvastatin, but was conducted independently by The Cleveland Clinic Cardiovascular Coordinating

Center. The results of the study were published in the March 3 issue of the *Journal of the American Medical Association*.

Bristol-Myers Squibb, the maker of pravastatin, criticized the research. The company argued that a halt in the growth of plaque was not necessarily the same as a reduction in heart attacks and deaths. It then funded Harvard Medical School researchers to prove that its drug treatment was as good as atorvastatin. And PROVE-IT they did, although not in the way Bristol-Myers Squibb would have liked.

The TIMI 22 study (Pravastatin or Atorvastatin Evaluation and Infection Therapy; PROVE-IT) enrolled 4,162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days. The researchers compared 40 mg of pravastatin daily (standard therapy) with 80 mg of atorvastatin daily (intensive therapy).

The study was designed to establish the noninferiority of pravastatin as compared with atorvastatin with respect to the time to an endpoint event. The primary endpoint was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. Follow-up lasted 18-36 months, with a mean of 24 months.

The median LDL-cholesterol level achieved during treatment was 95 mg/dL in the standard-dose pravastatin group and 62 mg/dL in the high-dose atorvastatin group. Atorvastatin showed superiority to pravastatin, resulting in a 16% lower risk of the primary endpoint.

Intensive therapy with high-dose atorvastatin had a consistent beneficial effect on cardiac events, including a significant 29% reduction in the risk of recurrent unstable angina and a 14% reduction in the need for revascularization. The reduction in clinical events with the more intensive lipid-lowering therapy was apparent as early as 30 days after the start of therapy. Patients treated with high-dose atorvastatin, however, had significantly more liver-related side effects than patients treated with standard-dose pravastatin.

The researchers conclude that "given the substantially lower LDL-cholesterol levels achieved in the group given 80 mg of atorvastatin daily [median, 62 mg/dL], our results suggest that after an acute coronary syndrome, the target LDL-cholesterol level may be lower than that recommended in the current guidelines."

Taken together, the REVERSAL and PROVE-IT trials herald a shake-up in the field, Topol says. "We know that atherosclerotic progression and clinical outcomes will be ameliorated by much more aggressive use of statins. Indeed, the 80 mg dose of atorvastatin is the most intensive LDL-lowering regimen for which data on clinical outcomes are available. Unfortunately, we do not know the precise mechanism of action responsible for atorvastatin's superiority." He suggests more investigation is needed to untangle the independent and interdependent effects of statins on LDL-cholesterol levels and the process of arterial inflammation.

One obstacle to a change to more intensive statin therapy would be cost. The recommended starting dose of atorvastatin is 10 mg per day. The cost at this dosage in Cleveland pharmacies is $900 per year, Topol says. The 80 mg dose costs $1,400 per year. "The statin drugs already account for the largest prescription drug expenditure in the United States, at $12.5 billion per year. Treatment based on the new data could cause the costs associated with

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).
Senior Production Editor: **Nancy McCreary**.

statin therapy to skyrocket even further."

Still, Topol predicts there will soon be a sea change in the prevention and management of atherosclerotic vascular disease. "The proportional reduction in major clinical outcomes that results from aggressive statin therapy is of the same order of magnitude as that seen when statins were compared with placebo in controlled trials. Intensive therapy with statins, monitored by means of measurements of LDL-cholesterol or biologic markers of inflammation, is likely to result in even greater steps toward actualizing the full benefit of this remarkable class of medicines." ■

Hospital develops unit-based pharmacist program

The switch results in 90%+ success rate

Computerized physician order entry (CPOE) may be one way to curb medication errors. The reality, however, is that most health care centers have not implemented such a program — and may never will. CPOE systems are expensive, and some professionals fear the technology will be outdated during the time it takes to install the system and teach staff to use it.

Instead, some hospitals are looking for other methods to decrease medication errors. John T. Mather Memorial Hospital in Port Jefferson, Long Island, NY, took the challenge and developed a system in which a clinical pharmacist works with staff on each patient-care unit and enters the medication orders directly from the patient's chart.

The unit-specific pharmacist program, which began in March 2001, has been the success that organizers had hoped. Pharmacist interventions continue to increase, 43% over the year 2002, says **Olga Larios**, MS, RPh, director of pharmacy. Nurses and physicians now consider pharmacists a trusted component of the patient care process.

In addition, the pharmacists have implemented a pharmacist-initiated intravenous (IV) to oral (PO) medication switch, which has had a success rate of more than 90%. This is quite an improvement from the 36% that researchers from Harvard Medical School recently reported using their CPOE system. **(See *Drug Formulary Review*, February 2004, cover page.)**

"On the outside, we are all in favor of CPOE," Larios says. "However, it's a huge monetary investment and it's not without its problem. We feel this program is a viable alternative to the CPOE that so few hospitals are utilizing right now."

Get everyone on board

The idea began in late 2000 as a response to the country's heightened awareness of medication errors, Larios says "Our administrative staff said it would like a response from our hospital. We thought about it and came up with this plan."

The program started as a pilot in a small area of the hospital to see how physicians and staff would receive it. After a few months, the medical board saw the validity of the program and agreed to add a full-time pharmacy staff member. "It took about six months from the early start of the program until we were in full swing," Larios says.

The 248-bed hospital has two main floors. The program involves having one pharmacist on each floor all day long. One floor, for example, has an intensive care step-down unit, a coronary care unit, a telemetry area, and a medical-surgical patient care area.

"Instead of physician order entry, we have pharmacist order entry of medications and laboratory orders," explains **Jeffrey Santorello**, MS, MLS, RPh, a clinical pharmacist who helped develop the program. "That pharmacist has access to laboratory data, nursing personnel, and medical personnel. We interact closely by the patient bedside with medication orders and questions that would pertain to medicine."

The program was not easy to start, Larios says. "You have to gain the respect and have the physician staff, in particular, know that you have the knowledge."

John T. Mather Memorial Hospital is not a teaching facility and therefore does not have residents and interns. "We deal strictly with an attending staff, which makes the hurdle a little more difficult in the beginning," she says. "However, we overcame it and quickly came to our present level [of trust]."

The pharmacy services department has a core of two or three pharmacists that it uses to work on the two floors. "Some pharmacists aren't comfortable being on the floor, and others are. We try to rotate the ones who are whenever we can," Santorello says. Three other pharmacists also are available to fill in on the floors when needed.

The floor-based pharmacists also got approval from the medical board and the pharmacy and therapeutics (P&T) committee to switch some medications from IV to PO without first getting physician approval. The pharmacists make the change directly on the chart, with the physician signing the change the next day.

In the beginning, pharmacy services evaluated how much money it thought it would save using one or two drugs, Santorello says. This part of the program continued once the department proved the switch was a cost-saving measure and that it could be done with the cooperation and the trust of the doctors.

Initially, the pharmacists started with about four medications, which were 100% bioavailable, and gradually increased the number over the years, Larios says. The nursing staff seemed to buy into the program quickly. They now give the clinical pharmacists the names of patients who need to have their medications switched from IV to PO.

The nursing staff even asked the pharmacists to expand the medication list to include five or six medications. In the last P&T committee, physicians asked if other medications could be added to the list, too. "It was an interesting source for the recommendation," she says.

Now the pharmacists have more than 10 medications that they are able to change from IV to PO according to protocol without contacting the physician. **(See the list, right.)** "Very rarely — maybe one or two cases a year, we have a physician who wants to keep the patient on IV another day," Larios says. The success rate of the switch has been up to 97%.

The program is unique in that the pharmacists don't call the physicians for most of the IV switches, Santorello says. "The clinical pharmacist does it automatically with permission from the pharmacy and therapeutics committee and the medical board. It is interesting that major hospitals don't have this program in effect, where the pharmacist goes from IV to PO when certain criteria are met."

The Harvard CPOE study found that physicians were hesitant to make the switch for certain patients, such as those in the intensive care unit (ICU). Having a pharmacist on the unit tends to bypass that problem, Santorello says. "[By seeing all the patients on the floor], we are able to monitor their drug therapy. If the patient is on total parental nutrition or is in the ICU or coronary care unit, we would be hesitant to make the change." Instead of spending time on the more questionable switches, the pharmacists instead go right to the ones they can change automatically, Santorello says.

The trust that allows physicians to feel comfortable with pharmacists making that change didn't happen overnight, he adds. "It was something that we developed."

Overall, the pharmacist presence at the bedside makes the program a success, he says. "Pharmacists being on the floor make this happen."

When he was first on the floor, nurses didn't really know how to approach him with questions. That has changed. "Nurses now depend on me for drug information and for problems involving patient medication. I feel I am part of the nursing team." ■

Medications approved switch from IV to PO

Here are the medications that clinical pharmacists at John T. Mather Memorial Hospital in Port Jefferson, Long Island, NY, can switch from IV to PO without first getting physician approval. (The hospital's medical board and pharmacy & therapeutics committee have approved the list.) The physicians sign the change on the chart the next day.

- Moxifloxacin (Avelox) 400 mg
- Ciprofloxacin (Cipro) 200 mg and 400 mg
- Fluconazole (Diflucan) 200 mg and 400 mg
- Metronidazole (Flagyl)
- Famotidine (Pepcid) 20 mg
- Pantoprazole (Protonix) 40 mg
- Gatifloxacin (Tequin) 200 mg and 400 mg
- Doxycycline (Vibramycin)
- Azithromycin (Zithromax) 250 mg
- Linezolid (Zyvox) 600 mg. ■

Testing shows women unaware of fracture risk

Project shows collaboration across continuum

Pharmacists in a recent project screened and counseled patients about their risk for bone fractures — and found that most of them (78%) had no knowledge of their risk prior to the screening.

Results of Project ImPACT: Osteoporosis suggest that "breakthrough" results are possible when patients, pharmacists, and physicians collaborate closely, using pharmacy-based testing to identify and refer patients who are at-risk, the project researchers say. Although the project involved community pharmacy-based testing, it has ramifications for hospital pharmacists who work with their patients on medication management and overall disease prevention.

"Pharmacists have a huge role in prevention activities," says **Jean-Venable "Kelly" R. Goode**, PharmD, BCPS, an associate professor at the Medical College of Virginia School of Pharmacy, Virginia Commonwealth University, in Richmond. She is the lead author of the paper that detailed the results of the study. The paper recently was published in the March/April 2004 issue of the *Journal of the American Pharmacists Association*.

"So many times we just respond to patients' drug treatment, when we can also look at their current medications and see the risks that they may have for other diseases," she says. For example, people who are on chronic steroids are at risk for osteoporosis. "We can counsel those patients so we can maybe prevent them having that problem in the future."

Project ImPACT: Osteoporosis is a demonstration project of the American Pharmacists Association (APhA) Foundation. The observational study was funded through a grant from Merck & Co.

The project was conducted in a regional supermarket chain in Virginia. Much of the project was held during Women's Health Month, Goode says. The project was promoted with in-store signs, shelf-talkers, and messages on grocery store receipts.

Project ImPACT: Osteoporosis had two phases. One focused on screening, patient education, and referral at key sites. The screening was not diagnostic, Goode says. Instead it looked at risk of future fracture. All patients paid $25 out-of-pocket for the pharmacy-based screening.

The project screened a total of 532 patients for osteoporosis between May 2001 and October 2002. Most of the patients were women (93%), with a mean age of 55.8 years. The risk stratification was 37% high risk, 33% moderate risk, and 30% low risk. All of the moderate and high-risk patients were referred to primary care and/or specialty practice physicians for appropriate diagnosis and treatment.

"One of the great things about being screened early for osteoporosis is that patients can start doing some preventive measures," Goode says. Based on the risk for future fracture, a pharmacist can appropriately counsel patients on the things they need to do to prevent osteoporosis, such as taking calcium and vitamin D supplements, doing weight-bearing exercises, and limiting caffeine and alcohol intake. Patients in a high- or moderate-risk category can be referred to their physician for diagnostic testing.

Opening the dialogue between physician and patient is a key component of preventing osteoporosis, Goode says. "Physicians have so much on their plate. They are [usually] looking at a primary problem during the visit. They don't always have the time to look at prevention activities."

The researchers also followed-up with more than half of the patients (305) through telephone interviews three to six months later. In the moderate- and high-risk categories, 30% and 42%, respectively, made physician office visits subsequent to the screening, and their physicians initiated 24% of these patients on new osteoporosis therapy.

The second phase of the study involves rollout of both screening and collaborative community health services for patients at risk for or with osteoporosis throughout the supermarket's customer service area. As part of this phase, the health plan UnitedHealthcare of the Mid-Atlantic is paying participating pharmacists for the collaborative community health management services provided to its members enrolled in this project.

The data from this project can help pharmacists realize they can make an impact on health-promotion activities, Goode says. "There are a lot of different things that pharmacists can become involved in for health promotion, osteoporosis being one of them. We can identify people at risk and refer them to their physicians for follow-up care. "We have a huge chronic disease burden in this country," she continues. "Many of those chronic diseases could potentially be prevented if people [took the preventive measures] earlier in life." ■

Fentanyl (Duragesic) recall is expanded

Janssen Pharmaceutica Products has expanded its recall of fentanyl transdermal system (Duragesic)

CII 75 mcg/hr, NDC #50458-035-05 from one lot to five. The control numbers are 0327192 (exp. 10/05), 0327193 (exp. 10/05), 0327294 (exp. 11/05), 0327295 (exp. 11/05), and 0330362 (exp. 12/05).

The company recalled one lot of Duragesic 75 mcg/hr patches (control number 0327192) in February 2004 after determining that a small percentage of patches in this lot might leak medication along one edge. Since then, a small number of patches with the same problem have been identified in one additional lot. As a precaution, the company is recalling four additional lots of 75 mcg/hr patches that were produced on the same manufacturing line during the same period.

Exposure to the leaked medication could result in inadvertent ingestion or increased transdermal absorption of the opiate component fentanyl, leading to potentially life-threatening complications. Conversely, leakage of medication could lead to inadequate dosing, resulting in treatment failure, and/or opiate withdrawal.

Anyone who comes in contact with the leaked medication is advised to rinse exposed skin thoroughly with water only; soap should not be used.

For more information about the recall, see www.fda.gov/cder/drug/shortages/duragesicLetter.pdf. ▼

Most hospital pharmacists monitor medication therapy

Almost all pharmacists in United States hospitals regularly monitor patients' medication therapy in some capacity, according to results of the 2003 ASHP (America Society of Health-System Pharmacists) National Survey of Pharmacy Practice in Hospital Settings. The survey, which was published in the March 1 issue of the *American Journal of Health-System Pharmacy,* focuses on the role pharmacists play in managing and improving the medication-use process.

The survey found that in the last three years, most hospitals have increased the amount of time pharmacists devote to monitoring patients' medication therapy. To facilitate pharmacists' involvement in medication monitoring, hospitals have undertaken a variety of activities, including:

- Hiring more clinical pharmacy staff.
- Granting pharmacists better access to computerized patient data.
- Implementing computerized prescriber order entry systems.
- Redeploying pharmacists to patient-care units.
- Expanding the responsibilities of pharmacy technicians.
- Implementing automated dispensing systems.
- Educating administrators on the impact of clinical pharmacy services on patient care.

Large hospitals were most likely to have increased pharmacist hiring and implemented technological advances to promote pharmacist patient-care involvement, but small hospitals were equally likely to have expanded technician responsibilities and pharmacist access to patient data to accomplish these same goals.

High-risk patients are most often the beneficiaries of pharmacists' medication-monitoring services. Patients in the intensive care unit were most likely to be monitored (81.6%), followed by patients being treated in the medical-surgical service (62.5%), nutrition service (46.8%), and pediatric service (38%).

In general, more than three-fourths of hospitals had pharmacists routinely monitor blood levels or other patient responses to medication. For example, nearly all hospitals had pharmacists monitor aminoglycosides and vancomycin (94.2% and 92.8%, respectively). Additionally:

- Just over 76% of hospitals had pharmacists monitor patient response to warfarin.
- 66.9% monitor response to heparin.
- 52.6% monitor phenytoin levels.
- 47.1% monitor theophylline levels. ▼

Study: Early treatment with thrombolytic t-PA for stroke

A study in the March 6 issue of *The Lancet* confirms the benefits of getting stroke patients to the hospital quickly for rapid thrombolytic treatment, according to the National Institute of Neurological Disorders and Stroke (NINDS), a part of the National Institutes of Health (NIH).

Stroke patients who were treated within 90 minutes of the onset of their symptoms showed the most improvement. The study suggests that t-PA given up to four hours after the onset of symptoms may be of benefit. As time passes, the effect of treatment seems to diminish. The researchers estimate there almost is no benefit when treatment is administered at six hours.

Another significant finding reported by the authors is that severe stroke patients tend to present to the hospital earlier than patients with milder

strokes, and those who were treated had much better recoveries than patients who were given a placebo. This means that the greatest effect of early treatment was seen in the group with the most to gain in terms of reducing long-term disability.

The pooled data from the trials — two were sponsored by pharmaceutical companies and one was funded by NIH — represent the work of 16 teams of researchers and several statisticians around the world. Although the data in *The Lancet* paper suggest that the beneficial effect of t-PA may extend beyond three hours (from 181 to 270 minutes), the authors caution that large prospective randomized trials would be required to confirm this finding and that this does not justify any delays in treatment. ▼

Sponsors announced for Medicare drug discount card

Health and Human Services (HHS) Secretary Tommy G. Thompson has announced the approval of 28 private sponsors to provide seniors and people with disabilities savings on their prescription drugs, beginning June 1. With the new cards, Medicare beneficiaries will receive discounts on prescription drugs, and low-income beneficiaries may receive an additional $600 to pay for their prescription medicines in both 2004 and 2005.

All Medicare beneficiaries, except those who already receive outpatient drugs through Medicaid, will be able to enroll in a discount card program starting in May. HHS says that the sponsors are planning to offer 48 general drug discount cards, 27 available nationally to all eligible Medicare beneficiaries. Thirty-six of the general cards will charge a fee of less than $30 to enroll in a card, including five that will not charge a fee. There is no enrollment fee for people who qualify for the $600 credit.

Medicare-approved cards will be marketed to seniors by organizations offering the cards. Seniors will sign up for the cards directly with the organization offering the card they choose. HHS will provide seniors help in selecting a card.

Under the prescription drug card program, approved cards must offer discounts on prescription drugs for all of their Medicare enrollees. At least some of these savings must come from manufacturer rebates. Card sponsors also must publish prices for the prescription drugs their cards will cover, provide access to an extensive retail pharmacy network, operate call centers, and have a process to respond to beneficiary concerns.

A list of Medicare-approved card sponsors is available at www.hhs.gov/news/press/2004pres/20040325.html. ■

New FDA Approvals

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

• *Cinacalcet (Sensipar) by Amgen*. The FDA has approved cinacalcet (Sensipar), a drug to treat **secondary hyperparathyroidism in patients with chronic kidney disease on dialysis, and hypercalcemia in patients with parathyroid cancer.**

Cinacalcet is the first drug in the class of calcimimetics to be approved by the FDA. Treatment with cinacalcet lowers serum levels of parathyroid hormone as well as the calcium x phosphorus ion product.

In three six-month cinacalcet clinical trials of more than 1,000 patients with chronic kidney disease receiving dialysis, the most commonly reported side effects were nausea and vomiting, which occurred in 31% and 27%, respectively, of cinacalcet-treated patients, compared with 19% and 15%, respectively, of patients who received placebo. Treatment of patients with chronic kidney disease with cinacalcet also was associated with the development of low serum calcium levels in a significant number of patients. Frequent monitoring of patients' calcium levels is therefore recommended in the cinacalcet labeling. ■

COMING IN FUTURE MONTHS

- Medicare to publish drug prices
- Iron complex evaluation
- A competency assessment tool for drug use policy and drug information
- Multitasking success in pharmacy practice
- Identifying serious drug-drug interactions

IN THE PIPELINE

• Delex Therapeutics has dosed the first patients in the company's Phase II clinical trial of aerosolized liposome encapsulated fentanyl (AeroLEF) in post-surgical patients. The objective of this study is to confirm the analgesic effects of aerosolized liposome encapsulated fentanyl in adult patients experiencing **moderate-to-severe pain following arthroscopic anterior cruciate ligament surgery reconstruction**.

• Nabi Biopharmaceuticals has announced that the FDA has determined that the company's investigational product, *Staphylococcus aureus* Immune Globulin (Human) (Altastaph) for immediate protection against ***S. aureus* infections in neonates**, has received a fast-track designation.

• Kosan Biosciences has announced the start of a Phase Ib clinical trial to evaluate KOS-862 (Epothilone D) as an anticancer therapy in combination with gemcitabine HCl (Gemzar) in patients with **advanced solid tumors**.

• Transkaryotic Therapies has announced that its clinical trial evaluating iduronate-2-sulfatase (I2S) has completed patient enrollment. I2S is TKT's investigational enzyme replacement therapy for the treatment of **Hunter syndrome** (MPS II).

• Inhibitex has begun enrollment in a Phase II clinical trial for Aurexis, a humanized monoclonal antibody being developed as a first-line therapy, in combination with standard of care antibiotics, for ***S. aureus* bloodstream infections in hospitalized patients**.

• Vion Pharmaceuticals has received fast-track designation from the FDA for VNP40101M (Cloretazine) in **relapsed or refractory acute myeloid leukemia**.

• Micromet AG has initiated a randomized, open-label, international, Phase II trial to investigate the efficacy and safety of fully human antibody MT201 for the treatment of **breast cancer patients who experienced a metastatic relapse**.

• Threshold Pharmaceuticals has begun a Phase I clinical trial of 2-deoxy-D-glucose (2-DG). 2-DG selectively targets the **slow-growing but highly metastatic cells within the poorly vascularized zones of solid tumors**.

• Amicus Therapeutics has announced that the FDA has granted orphan-drug status for the company's first clinical candidate, AT1001, for the treatment of **Fabry disease**.

• EntreMed has announced that a new formulation of 2-Methoxyestradiol, 2ME2 (Panzem) currently is being evaluated in a Phase I clinical trial. 2-Methoxyestradiol, 2ME2 has been tested in **cancer patients** as a single agent, as well as in combination with chemotherapeutics.

• NeuroMed Technologies has initiated Phase I clinical testing for its lead drug candidate, NMED-160 (a calcium channel blocker) for **chronic pain**.

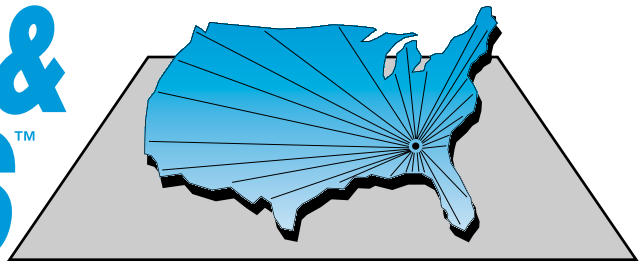
• Panacos Pharmaceuticals has begun a Phase I clinical trial of its **small molecule HIV drug candidate PA-457**.

• Pharmos Corp. has completed patient enrollment in its Phase III study of dexanabinol for the treatment of **severe traumatic brain injury**.

• Targeted Genetics has initiated a Phase I clinical trial of its product candidate, tgAAC94, in patients with **rheumatoid arthritis**.

• Genmab A/S announced that HuMax-CD4, an antibody that targets the CD4 receptor on T-lymphocytes, has been designated a fast-track product by the FDA. This designation covers patients with **cutaneous T-cell lymphoma** who have failed currently available therapy. ■

DRUG CRITERIA & OUTCOMES™



Aprepitant (Emend) Formulary Evaluation

Mechanism of Action, Indications, Special Populations, Adverse Reactions, Drug Interactions, and Precautions

By **Omar Dudar**, PharmD candidate
Harrison School of Pharmacy
Auburn (AL) University
Written while on clinical rotation at Huntsville (AL) Hospital

Drugs used in combination:
Dexamethasone (Decadron) — Merck
Ondansetron (Zofran) — GlaxoSmithKline
Granisetron (Kytril) — Roche

Mechanism of action

Aprepitant (Emend) is unique from other drugs used for chemotherapy-induced nausea and vomiting (CINV) in that it is a selective antagonist of substance P/neurokinin 1 (NK_1) receptors. Aprepitant has negligible affinity for other anti-emetic directed receptors such as serotonin ($5\text{-}HT_3$), dopamine, and corticosteroid targets. Aprepitant is capable of penetrating the central nervous system (CNS) and passing the blood-brain barrier to bind with NK_1 receptors.

Blockade of the $5\text{-}HT_3$ receptors by ondansetron and granisetron antagonize effects of enterochromaffin cell release of serotonin resulting from chemotherapy treatments. Interruption of the stimulus of neurotransmitters to the chemotrigger zone in the fourth ventricle of the brain will help to block the resultant triggering of the salivation center, and respiratory, pharyngeal, gastrointestinal (GI), and abdominal muscle contraction leading to vomiting.

Together with dexamethasone and ondansetron, aprepitant has been shown in studies to act synergistically to inhibit both the acute and delayed phases of highly emetogenic chemotherapy such as cisplatin-related emesis.

Pharmacokinetic profiles of aprepitant and ondansetron are summarized in **Table 1.**

Table 1: Phamacokinetics

Variable	Aprepitant	Ondansetron
Bioavailability	60-65%	56-71%
t_{max} (time to reach maximum serum concentration)	4 hours	Oral administration: 1-2.2 hours Intravenous (IV) administration: end of infusion
$T_{½}$ (terminal half-life)	9-13 hours	3-5.5 hours
Dose	125 mg day 1 180 mg days 2-3	Single IV 32 mg, or 0.15 mg/kg over three doses with cisplatin
Clearance	62-90 mL/min	600-700 mL/min
Excretion	57% urine, 45% feces	44-66% renal 25% feces
Metabolism	Hepatic CYP3A4, 1A2, 2C19	Hepatic CYP3A4
Protein binding	95%	70-76%
Dosage form	Capsule	Tablet, IV, suppository

Indication and dosage

Aprepitant is used in combination with dexamethasone and granisetron for acute and delayed nausea and vomiting due to highly emetogenic agents such as cisplatin and cyclophosphamide. Anticipatory emesis starts before administration of chemotherapy; acute emesis occurs within a few hours after starting chemotherapy, while delayed emesis starts after a day after chemotherapy. Aprepitant is given as a three-day regimen along with a corticosteroid and a 5-HT_3 antagonist. The recommended dose of aprepitant is 125 mg one hour before beginning chemotherapy on the first day, and is combined with oral dexamethasone 12 mg and ondansetron 32 mg IV.

Dexamethasone 8 mg is given with each dose of 80 mg aprepitant for days 2 and 3. Ondansetron also is used separately or in combination with a corticosteroid for postoperative and radiation-induced nausea and vomiting. It is given as a single 32 mg IV dose or three 0.15 mg/kg doses intravenously for CINV. It is also available in a 4 mg dose to be administered over 2-5 minutes for postoperative prevention of nausea and vomiting.

Special populations (aprepitant)

Gender:

- Aprepitant has a 16% higher C_{max} (maximum serum concentration) in females compared to males.
- Half-life is 25% lower in females.
- No dosage adjustment is necessary for differences.

Geriatric:

- Area under the curve $(AUC)_{0\text{-}24h}$ was 21% higher on day 1 and 36% higher on day 5 for elderly patients 65 years or older.
- No dosing adjustment is necessary.

Race:

- $AUC_{0\text{-}24h}$ is 25% and 29% higher in Hispanics vs. whites and blacks, respectively.
- C_{max} is 22% and 31% higher in Hispanics compared to whites and blacks, respectively.
- No dosing adjustment is necessary.

Hepatic and renal insufficiency (aprepitant):

- No dosing adjustment due to clinically insignificant increases in $AUC_{0\text{-}24h}$ for mild-to-moderate hepatic and renal insufficiency.
- No dosage adjustment is necessary for aprepitant in severe renal insufficiency (creatinine clearance [CrCl] < 30 mL/min) and patients with end-stage renal disease (ESRD) requiring dialysis.
    - In patients with severe renal insufficiency and ESRD on dialysis, the C_{max} decreased by 32% compared to healthy subjects.
        - — In severe renal insufficiency, AUC

Table 2: Patients with adverse reactions of 3% or more

Adverse event	Aprepitant (n = 544)	Standard therapy = dexamethasone and ondansetron (n = 550)
Abdominal pain	4.6%	3.3%
Asthenia/fatigue	17.8%	11.8%
Dehydration	5.9%	5.1%
Dizziness	6.6%	4.4%
Fever	2.9%	3.5%
Mucous membrane disorder	2.6%	3.1%
Constipation	10.3%	12.2%
Diarrhea	10.3%	7.5%
Epigastric discomfort	4.0%	3.1%
Gastritis	4.2%	3.1%
Heartburn	5.3%	4.9%
Nausea	12.7%	11.8%
Vomiting	7.5%	7.6%
Tinnitus	3.7%	3.8%
Neutropenia	3.1%	2.9%
Anorexia	10.1%	9.5%
Headache	8.5%	8.7%
Insomnia	2.9%	3.1%
Hiccups	10.8%	5.6%

decreased by 21%.
    - — In ESRD patients undergoing dialysis, AUC decreased by 42%.
  - Although the AUC of total aprepitant (bound and unbound to protein) and C_{max} decreased in both cases above, subsequent decreases in protein binding of aprepitant restore pharmacologically active unbound drug levels.
  - Formulary packet information indicates the resultant AUC of pharmacologically active unbound drug was not significantly affected in patients with renal insufficiency compared to healthy patients.
- There are no studies in severe hepatic insufficiency for recommendations of dosing changes.

Ondansetron: Do not exceed a total daily dose of 8 mg in severe hepatic dysfunction.

Adverse reactions

Adverse events were reported in 69% of 544 patients treated with aprepitant vs. 68% of 413 patients in the standard group. The most common adverse events of the aprepitant group were asthenia, headache, dizziness, constipation, diarrhea, abdominal pain, and anorexia **(see Table 2)**. Hiccups and fatigue were more common with aprepitant-tested patients than standard therapy.

Drug interactions/precautions

Aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4 enzyme. Aprepitant also has demonstrated induction of CYP2C9 enzyme. Although aprepitant's inhibition of CYP3A4 enzymes causes increases of other drugs metabolized by the CYP3A4 enzyme system, dosage adjustments of aprepitant were not made in trials.

Aprepitant's concentration will greatly increase when given in addition to CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, and ritonavir). It is important to avoid administering aprepitant with known inducers of CYP3A4 (rifampin, carbamazepine, and phenytoin.) As an example of aprepitant's induction of CYP2C9, levels of drugs such as the S-warfarin isomer and phenytoin may be lowered.

Ondansetron is a substrate for CYP1A2, 2D6, and 3A4, so inducers (rifampin, carbamazepine, clarithromycin) and inhibitors (cimetidine) of these enzymes will affect the levels of ondansetron. Ondansetron will decrease the analgesic effect of tramadol when used in combination. Ondansetron will decrease levels of cyclophosphamide when coadministered.

A list of drugs that interact with aprepitant therapy and the clinical effects of the interaction can be found in **Table 3**.

Ondansetron interactions ↑QT_c interval: Adenosine, antipsychotics (drug class), astemizole, bepridil, cisapride, clarithromycin, anti-arrhythmic agents (Class I and III), clindamycin, erythromycin, and fluconazole.

Table 3: Aprepitant drug interactions

Drug	Aprepitant
Ondansetron or granisetron	• No clinically important effects on kinetics of 5-HT_3 antagonists.
Dexamethasone	• Increases AUC of dexamethasone.
Methylprednisolone	• Aprepitant inhibits metabolism. • IV dose of methylprednisolone should be reduced 25%. • Oral (PO) dose of methylprednisolone should be reduced 50%.
Tolbutamide	• Decreases levels of tolbutamide due to induction of CYP2C9.
Oral contraceptives	• Decreases AUC of oral contraceptives (need alternative form of contraceptive) probably due to enzyme induction of CYP3A4.
Midazolam	• Increases plasma concentration of midazolam due to inhibition of CYP3A4.
Diltiazem	• Increases aprepitant plasma concentration x2. • 1.7-fold increase in diltiazem AUC. • No clinical significant changes in heart rate, blood pressure, or ECG.
Rifampin	• Aprepitant decreases AUC by 11-fold and half-life shortens x3 due to rifampin's enzyme induction.
Ketoconazole	• Increases AUC of aprepitant 5x and half-life prolonged x3 through ketoconazole's inhibition of CYP3A4.
Warfarin	• Aprepitant's induction of CYP2C9 causes decreases in S-warfarin concentration. • Monitor international normalized ratio (INR) for 7-10 days following start of aprepitant.

Table 4: Cocquyt et al prevention of emesis between groups

Phase	Aprepitant IV	Ondansetron 32 mg IV	P value
Acute phase			
Patients with no emesis	37%	52%	No significant difference between groups
Delayed phase			
Patients with no emesis	72%	30%	P = 0.005

Summary: QT_c interval prolongation is not a class-wide effect with the notable exception of granisetron. Dolasetron, however, produces prolongation of the QT_c interval to the same extent as ondansetron.

Contraindications: Do not use aprepitant concurrently with CYP3A4 metabolism-dependent drugs such as pimozide, terfenadine, astemizole, or cisapride due to the increased possibility of QT_c interval prolongation and risk of cardiac arrhythmias.

Ondansetron: Contraindicated if there is a hypersensitivity to 5-RAs.

Pregnancy/lactation

Aprepitant and ondansetron:

- Category B.
- No impaired fertility or harm to fetus known at this time.
- Excreted in the milk of rats.
  - No tests in humans.
  - Recommendation to stop breast-feeding or stop drug.

Possible medication errors with aprepitant

- Giving aprepitant at two different doses (125 mg on day 1 and 80 mg days 2 and 3).
- Specifying dosing times: Administer 125 mg aprepitant one hour before chemotherapy on day 1, and then patients receive 80 mg aprepitant once a day on days 2 and 3.
- Treating with aprepitant for more than three days.
- Using aprepitant with standard therapy for less highly emetogenic drugs.
- Giving aprepitant to stop an acute onset of vomiting. ■