AMERICAN HEALTH CONSULTANTS®

DRUG UTILIZATION REVIEW™

Pharmaceutical Care Across the Continuum

IN THIS ISSUE

AUGUST 2001

VOL. 17, NO. 8 (pages 57-64)

Expensive drugs 'bust' pharmacy budgets: Is there any recourse?

Guidelines for use, assistance programs provide some control

Lynn Uber, PharmD, was concerned when she saw a form from a physician requesting the drug NovoSeven (recombinant human coagulation Factor VIIa). The Medical University of South Carolina (MUSC) in Charleston, where Uber is a clinical associate professor and helps oversee pharmacy contracts, is an indigent care center, and the patient needing this drug had no insurance.

NovoSeven is expensive; one course of treatment costs about $100,000. Uber contacted the physician, who said the situation was life-or-death. The patient ended up receiving the drug and subsequently has been back in the hospital for a second course of therapy.

"At the end of the year, this drug could break the $1 million mark on its own," Uber says. "That's cost, not charge."

The financial impact of NovoSeven caught Uber by surprise. She's not alone in being caught off-guard by the cost and utilization of a drug. Most pharmacists are struggling to pay for drugs that can "bust" their budgets but improve patient outcomes.

The expense can happen in several different ways, says **Daniel Albrant**, PharmD, president of Pharmacy Dynamics, a health care consulting business based in Arlington, VA. "Any time a new drug comes out, it is always expensive, depending on the market forces. If the drug is a first compound in a class or a brand-new type of agent that everyone is excited about, the market will bear a higher price. A significant period of time will pass before there is any competition; you won't have the options for price shopping." *(Pharmacists may discover that taking a wait-and-see approach to using new drugs could reap both financial savings and improved patient outcomes. See story, p. 59.)*

At the same time, many pharmacists responsible for purchasing the drug are receiving pressure from physicians to buy it. "[They might say], 'If you don't get it, you are ethically negligent,'" Albrant says. "It doesn't matter what your budget says." Pharmacists also can be required by the government to offer a certain drug, such as Prevnar, the pneumococcal 7-valent conjugate vaccine for children, without being offered any options for paying for it, some pharmacists say.

In other situations, pharmacists have entire categories of expensive compounds to use, as in the realm of cancer chemotherapy, where many of the compounds have received FDA approval within the last few years and are the standard of care for different cancers. "Then the compounds are combined, so you may be using two or three, maybe four, expensive agents in one patient every month or so. It may go on for many months to years," says Albrant. "You get a situation where not only are you spending a lot of money, but you are spending a lot of money consistently."

Because MUSC also is a transplant/oncology center, Uber faces this problem. "If you look at our top 25 drugs, you would see a lot of transplant drugs and a lot of oncology drugs," she says. "They eat up a ton of our budget."

The surprise factor of a new drug can present a tough budgetary issue, as well. "Until the product is approved by the Food and Drug Administration (FDA), launched by the drug company, and is available for use from the wholesaler, you don't know how much it is going to cost," Albrant says. "You don't have an idea of what the utilization is going to be. You don't know if you are going to use it in one patient a month or 100 patients a month. That takes a while to figure out. So you can't predict the impact from a budgetary standpoint."

Even a lower-cost drug can make a dent in the budget if it has a high utilization rate. At MUSC, albumin use got out of control. "People used albumin instead of normal saline because it was there," notes Uber. The institution regained control by implementing strict use guidelines.

Guidelines for use are just one way pharmacists try to cover the cost of expensive drugs. To see what drugs might benefit from such guidelines, Uber first has to identify which drugs are causing the problems. Some she finds through her yearly report, which she runs to determine the top drugs used at the institution and the amount spent on them.

One problem drug Uber found through her report was iohexal. The increased cost of the contrast dye used in diagnostic medical imaging meant that the institution was running more tests. "We are taking a look at that to see if we can either get a better price or if we can reduce the number of tests," Uber says. "It's hard, however, to get physicians not to do tests."

Uber runs these reports as part of MUSC's Pharmaceutical Outcomes Management Program. The program, which she heads, is made up of teams from different specialties. Each team reviews the charges from its area and looks to see if it can improve its outcomes. The teams also have access to UHC (University of HealthSystem Consortium) benchmarks. These benchmarks allow the teams to compare their charge data to other hospitals, even analyzing it by individual procedures, says Uber.

The impact of a drug such as nonformulary NovoSeven was obvious the minute the order request was made. After the cost of the drug "hit a nerve," Uber says, guidelines for use were under development and now require physicians to obtain special permission before the first dose is dispensed. "That means checking for appropriate use and financial burden to the patient and institution," she explains.

If no insurance or government assistance is available, pharmacists sometimes turn to indigent care replacement or patient assistance programs. "If an unfunded patient gets the drug, the drug company will replace the drug for no cost," explains Uber. MUSC is in the process of setting up an indigent care replacement program for its expensive drugs. *(To learn where to find information on these programs, see p. 60.)*

Other measures that MUSC has taken to control drug costs include capitalizing on:

- **Volume-driven contracts.**

"If there are two or three drugs that are considered therapeutically equivalent, it behooves the hospital to get the best price on one and make it the preferred drug on the formulary," Uber says.

- **Generic drugs.**

"If there is an AB-rated generic substitution, then we purchase it," she says. "That's another way you can help to control costs these days." ■

COMING IN FUTURE MONTHS

- An in-depth look at the new patient safety standards
- A cost-cutting success story
- HHS offers guidelines on the HIPAA privacy rule
- Telepharmacy service gives 24x7 pharmacist call center support
- ASHP proposes "Medication Safety Officer" position

The new drug is out: Should you order it now?

Real-world use could expose hidden results

The new drug is available for use, and your physicians are eager to try it. Do you dare wait a few months to place your order?

It's the smart thing to do — waiting will save you money and may improve overall patient outcomes, says **Daniel Albrant**, PharmD, president of Pharmacy Dynamics, a health care consulting business based in Arlington, VA.

Albrant is not suggesting that a pharmacist deny a dying patient a new life-saving drug. Rather, he is suggesting that pharmacists consider the impact of real-world use on the effectiveness of a new drug.

Albrant advises his clients to wait six months or more before implementing many new drugs. "There is always something hidden," he says. "It's usually an adverse effect. Or it really doesn't work as well as it did in the trial because of the vagaries of real-world clinical practice. Or there is an immense learning curve with the drug, and there are a lot of errors."

Promptly using a new antibiotic is probably pretty safe, but some of the newer, more potent compounds have less room for error, continues Albrant. "It has been proven time and time again in my 15 years of practice that if you wait, it's always better for your patient than it is to jump on the bandwagon and use every new thing that comes along. There's always something that crops up that wasn't seen in the clinical trials."

A look toward Lilly's new sepsis drug

One drug that Albrant views with caution is Indianapolis-based Eli Lilly and Co.'s new drotrecogin alfa (activated), which is still under priority review by the Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research for the treatment of sepsis with associated acute organ dysfunction.

The drug, recently given the brand name Xigris, was granted the priority review after promising results from the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial. The results of the trial were published in the March 8, 2001, issue of the *New England Journal of Medicine* (344:699-709).

The buzz is strong on this drug, and many expect it to be a blockbuster. **Lynn Uber**, PharmD, clinical associate professor at the Medical University of South Carolina in Charleston is concerned primarily about its cost. "The drug hasn't even hit the market, and we are already working on guidelines for use," she says. "We know we are going to use it. It's just a matter of who is going to get it."

Uber has heard that it might cost about $10,000 for a course of therapy. "If every patient who is septic in the unit gets it, that will kill our budget," she notes.

The approval process has hit a bump, though. On June 13, Lilly announced that the FDA has extended the action date from July 27 to Oct. 27, 2001, for the completion of its review of the drug's biologics license application. Yet the company expresses confidence that the extension of the action date does not signify concerns about the drug's approvability.

Albrant thinks otherwise; serious bleeding events were the most common serious adverse effect found in the drug's trial. "I don't think the FDA will allow it to come out," he predicts.

The main problem with studies on sepsis drugs is that the population chosen in the study is amorphous, he says. "It's hard when it's not being used under a study protocol to find those same patients."

These types of drugs are not easily put into use in the general population, he says. "According to the FDA's language, once a drug gets approved for use for an indication, physicians can use it for anything — based on their best judgment. The thing that scares us the most about drugs for major infection is that they are typically targeted at specific cellular components or sometimes at the bacteria themselves." A physician, however, may think a patient is sick enough from the flu to try the drug, although the drug was never studied in that population and might not work.

Albrant and Uber take a different position on the drug's odds. "If I were septic and there was a chance that it would help, I would want that drug," Uber says.

Albrant, however, is concerned that the drug has been shown to have only a 6% absolute reduction in mortality. "That means that if we give 100 patients that drug, we make a difference in six of those patients. We don't make a

difference in 94 of those patients, but we still spend the money," Albrant points out.

"Whatever amount of money is spent on the drug, whether it is $100, $1,000, or $10,000, we are still using it 94 times out of 100 based on the pivotal trials that are at the FDA now. And you are not making an effect. You may even be inducing an adverse effect. When you are doing that, not only is it costing you the amount of the drug, but now it is costing you an increased length of stay in the hospital and increased utilization for all of the other services," argues Albrant. "There are some added and potentially hidden costs that the system bears that the pharmacy may or may not bear."

These same issues should be addressed with other chemicals, too, Albrant says. "We don't really have broad-enough studies or studies that replicate true clinical practice, so we can't predict the therapeutic effects — or the adverse effect profile.

"That's where we get burned a lot of times as a system," he continues. "It's easy to eat up a lot of your health care dollar by doing these things when we don't really understand the outcome and ramifications of use. We won't know that usually for two to three years."

Albrant knows many physicians are eager to try the new drugs. He suggests that pharmacists advise them about the drug's associated costs and how they relate to other financial needs of the institution. "[I would advise saying to them], 'Let's evaluate the cost impact and what our usage pattern is going to be, so we can predict what we need to do as a system and as an institution.'" He also would recommend waiting to see what happens with the drug in real-world use. *(For another example of the potential benefits of adopting a wait-and-see attitude on new drugs because of the impact of real-world use, see the story of a promising oral treatment for patients with chronic myeloid leukemia, p. 61.)*

If the physicians prefer not to wait to order the drug, Albrant suggests developing a protocol for use and perhaps limiting the drug's use to a few physicians in a specialty. "These kinds of restrictions are more common today, although they certainly are not universal," he says.

Some larger systems are making the ordering process for expensive drugs similar to that of a capital request. This means that the request might have to be approved by the finance committee, the medical executive committee, and the board of directors. These kinds of barriers make physicians realize that the request has an impact, Albrant says. "Then they make better decisions overall and patients don't suffer for the most part."

Fortunately, most compounds that come out of the FDA are not revolutionary, says Albrant. "From a purely clinical perspective, most are the evolution of products that we already have." ■

Find help defraying some medication costs

Web sites detail drug company programs

Pharmacists looking for ways to pay for the prescription medications of indigent patients often have turned to pharmaceutical manufacturers' medication assistance programs.

Pharmaceutical manufacturers typically offer three types of assistance programs to help these patients obtain either the medications or insurance coverage to pay for them, say researchers from the College of Pharmacy at the University of Georgia in Athens and the Medical College of Georgia in Augusta. Their study, "Medication assistance program for uninsured and indigent patients," was published in the June 15, 2000, issue of the *American Journal of Health-System Pharmacy* (57:1131-1136).

Most programs provide free prescription medications to patients who meet specific financial criteria, the researchers say. These criteria include not qualifying for third-party-payer assistance or having insufficient income or assets to afford medications, the guidelines of which are established by the company. Some programs help determine the scope of a patient's insurance coverage for medications, help identify billing problems, and attempt to resolve claim denials, they add. Still other programs offer payment-limitation programs for expensive and long-term medications. In these programs, the pharmaceutical company pays all costs exceeding a limit predetermined by the company.

Finding information, though, can be challenging. Here are four free web sites that can help facilitate access to patient assistance programs:

- **http://www.RxAssist.org**

This site was developed by Volunteers in Health Care, a not-for-profit organization based

in Pawtucket, RI, that focuses on indigent-care issues. The site provides information for about 100 pharmaceutical manufacturer programs that usually offer a limited supply of free prescription medication to eligible patients. Providers can search the RxAssist database by company name, brand name, generic name, or drug class. On-line forms are available for more than 40 companies and can be viewed and printed. RxAssist is updated continuously and recently added free patient tracking software, which is available to institutions on a CD-ROM or 11 floppy disks.

• **http://www.NeedyMeds.com**

This web site is managed by a patient advocacy group. The site includes links to the manufacturer's web site for specific drugs, if the manufacturers have them. There is no charge to the web site, but a printed manual is available at a cost of $99.95.

• **http://www.RxHope.com**

This web site is supported by venture capitalists and the Pharmaceutical Research and Manufacturers of America (PhRMA) in Washington, DC. The site provides on-line application forms that are submitted directly to the pharmaceutical company for processing. The web site retains patient information, has a tracking system, and minimizes mistakes by confirming that all form fields are completed correctly. Please note that the use of RxHope.com is limited to prescribers, certain advocacy organizations, and safety net hospitals.

• **http:// www.PhRMA.org/patients**

Member companies of the Pharmaceutical Research and Manufacturers of America (PhRMA) created this directory. The directory lists company programs that provide drugs to physicians whose patients could not otherwise afford them. The programs are listed alphabetically by company. Under the entry for each program is information about how to make a request for assistance, which prescription medicines are covered, and basic eligibility criteria.

Other sites require a fee, such as:

• **http://www.MedDataServices.com**

This site provides information and forms necessary to access more than 145 pharmaceutical manufacturers' patient assistance programs. It has the ability to upload patient and doctor profiles into the system that can be used to automatically fill out the forms. A tracking module also is offered. A monthly fee is required. ■

Gleevec available to treat chronic myeloid leukemia

But mutation may result in resistance to drug

In less than three months, the Food and Drug Administration (FDA) approved a promising oral treatment for patients with chronic myeloid leukemia (CML). At the time, researchers still wondered about the long-term effects of the drug, imatinib mesylate (Gleevec), also known as STI-571. Now some researchers have found that the gene responsible for CML can adapt to avoid the inhibitory effects of the drug.

Gleevec, developed by East Hanover, NJ-based Novartis, became available in mid-May. Gleevec is a new type of cancer drug that has a "rational" drug design. It is a protein-tyrosine kinase inhibitor that blocks the constitutive kinase, BCR-ABL, which is created by the Philadelphia chromosome, a genetic defect common among patients with CML.

The FDA put the drug under its accelerated approval program of drugs for serious or life-threatening diseases based on results from three international, open-label, single-arm Phase II studies that included 1,027 patients diagnosed with Philadelphia-chromosome CML. Patients in the chronic phase of the disease showed a hematologic response of 88%; 63% of those were in the accelerated phase and 26% were in the myeloid blast crisis phase. Side effects reported in the trials include nausea, vomiting, edema, muscle cramps, skin rash, diarrhea, heartburn, and headache. Severe fluid retention occurred in up to 2% of patients. (For complete prescribing information and clinical trial results, visit http://www.pharma.us.novartis.com/product/pi/pdf/gleevec.pdf.)

Charles Sawyers, MD, a researcher and oncologist at the Jonsson Cancer Center at the University of California-Los Angeles, was the lead researcher in Gleevec trials for all three phases of the disease. The initial results were incredible to see, he says. "It's absolutely amazing that just a pill with minimal side effects could be so dramatic."

But Sawyers did find that some patients developed resistance. "If patients have the advanced forms like blast crisis, they can develop resistance within about three months."

A recent study, published in the June 22 issue of *Science* (292:2231-2233) examined the relapse of

advanced-stage CML patients who initially had responded to Gleevec. In all cases examined, the researchers found that the drug resistance was associated with reactivation of BCR-ABL signal transduction. "These studies provide evidence that genetically complex cancers retain dependence on an initial oncogenic event and suggest a strategy for identifying inhibitors of STI-571 resistance," the researchers say.

Combination therapy key

In patients who show resistance, the drug needs to be used in combination therapy, says Sawyers. Jonsson Cancer Center is actively trying to enroll patients in combination studies that combine Gleevec with different types of chemotherapy, depending upon the patient's stage of disease. The Center now is holding two or three combination trials, in addition to continuing to follow the patients who are on Gleevec alone.

For the patients using only Gleevec, the question is how long do the responses to the drug last, Sawyers says. "Are they permanent, or will patients develop resistance even when they have the early stage? We don't know the answer because the drug is too new. It's important that we continue to collect the information on these patients."

Gleevec, which Novartis says will cost $2,000-$2,400 per month for the average patient (the company does offer a patient assistance program for the drug), also was shown to be helpful in the treatment of gastrointestinal stromal tumor, Sawyers says. "That's because those patients have a key mutation in an enzyme that is related to ABL, called KIT."

According to the June 2001 issue of *The Oncologist*, trials are under way in prostate cancer, lung cancer, glioma, and in other tumors overexpressing platelet-derived growth factor receptor (PDGF) receptor or c-KIT. "It should and will be tested against other tumors expressing c-KIT and PDGF receptor, and is likely to work against chronic monomyelocytic leukemia, in which the c-KIT receptor is overexpressed," says **Bruce A. Chabner**, MD, editor-in-chief of the journal, in an editorial.

The Oncologist contains an article by researchers at Oregon Health Sciences in Portland that presents previously unpublished information regarding the drug's pharmacokinetics: its reliable absorption, long half-life, and limited acute and chromic toxicity (6:244-238). Although Chabner acknowledges that researchers still do not know if the drug's CML control is permanent or temporary, his editorial brims with excitement about the drug.

"In conclusion, ST1571, or Gleevec, represents a monumental leap forward in cancer chemotherapy," Chabner writes. "It proves a principle. It justifies an approach. It demonstrates that highly specific, non-toxic therapy is possible."

[Editor's note: Look for more detailed information on Gleevec in an upcoming issue of Drug Criteria and Outcomes.*]* ■

NEWS BRIEFS

ASHP wants FDA mandate for drug barcoding

The American Society of Health-System Pharmacists (ASHP) in Bethesda, MD, has urged the Food and Drug Administration (FDA) to require drug manufacturers to print bar codes on all drug packages as a way to increase patient safety in hospitals and health systems nationwide.

In a letter to Tommy G. Thompson, secretary of the U.S. Dept. of Health and Human Services, ASHP stressed the immediate need for regulations requiring standardized machine-readable codes on all drug product containers, including single-dose medication packages used in hospitals. ASHP has concluded that manufacturers will not add codes to all medication packages in the foreseeable future without a federal mandate.

"When hospitals know that standardized bar coding will be required on medication packages, we believe that they will move quickly to have scanners ready at patients' bedsides," says **Henri R. Manasse Jr.**, PhD, ScD, executive vice president and CEO of ASHP. In addition to improving

patient safety, bar coding also would improve the efficiency of drug product purchasing, storage, and distribution in hospitals, allowing more time for pharmacists to help counsel patients and monitor drug therapy regimens, the society says. ▼

Expect flu vaccine delays for 2001-'02 season

About 64% of the 83.7 million influenza vaccine doses for the upcoming flu season will be available by the end of October, according to federal health officials during a regular meeting of the Advisory Committee on Immunization Practices (ACIP) in June. The remaining doses will be available in November and December. The officials say, however, that these early projections from manufacturers could change.

The ACIP made the following recommendations regarding flu vaccination strategies for health care providers for the upcoming flu season:

- Target vaccine available in September and October to those at increased risk of influenza complications and to health care workers.
- Continue vaccinating, especially those at high risk and in other target groups, through December and as long as vaccine is available.

For more information about federal recommendations and updates on influenza vaccine supply, visit the web site http://www.cdc.gov/nip/flu. ▼

Prostate cancer treatment may cause bone loss

Men may lose bone at an alarming rate as a result of a commonly used treatment for prostate cancer, say researchers at the University of Pittsburgh Medical Center (UPMC) and Beth Israel Deaconess Medical Center in Boston. The findings, published in the June issue of the *Journal of Clinical Endocrinology and Metabolism* (86:2787-2791), suggest that gonadotropin-releasing hormone agonists (GnRH-a), a frequently used treatment for prostate cancer, causes severe drops in bone mass and results in an increased risk of fracture in men.

The men who were treated with GnRH-a for prostate cancer experienced up to a decade's worth of bone loss within the first year of therapy, says senior author **Susan Greenspan**, MD, professor in the divisions of endocrinology and geriatric medicine in the department of medicine at the University of Pittsburgh. Physicians have been using GnRH-a for more than a decade to treat men with late-stage metastatic prostate cancer. Greenspan is concerned about GnRH-a now being used to treat more men with earlier-stage disease and for longer periods of time.

"In treating men with this therapy earlier and for longer periods of time, we are putting them in a menopause-equivalent condition and subjecting them to severe osteoporosis — a disease that may have more serious consequences than early-stage prostate cancer," she says. ▼

Drug Utilization Review™ (ISSN# 0884-8998), including **Drug Criteria & Outcomes**™, is published monthly by 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 Utilization Review**™, P.O. Box 740059, Atlanta, GA 30374.

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Subscription rates: One year (12 issues), $435. Outside U.S., add $30 per year, total prepaid in U.S. funds. Two to nine additional copies, $348 per year; 10 to 20 additional copies, $261 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 $73 each. (GST registration number R128870672.)

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JCAHO adopts new patient safety standards

New patient safety standards adopted by the Joint Commission on Accreditation of Healthcare Organizations will require hospitals to make specific efforts to prevent medical errors — and to notify patients when they have been harmed during treatment.

"Very simply, patient safety needs to be Job 1 for hospitals across the country and that's what our standards are seeking to do," says **Dennis O'Leary**, MD, president of the Oakbrook Terrace, IL-based Joint Commission.

"We need to create a culture of safety in hospitals and other health care organizations, in which errors are openly discussed and studied so that solutions can be found and put in place," he continues. "These new standards are intended to do just that."

The new standards encourage the internal reporting of medical errors, and actively engage clinicians and other staff in the design of remedial steps to prevent future occurrences of these errors. The additional emphasis on effective communication, appropriate training, and teamwork found in the standards language draw heavily upon lessons learned in both the aviation and health care industries.

Prospective analysis and redesign

A second major focus of the new standards is on the prevention of medical errors through the prospective analysis and redesign of vulnerable patient care systems, such as the ordering, preparation, and dispensing of medications. Potentially vulnerable systems can be identified readily through relevant national databases such as the Joint Commission's Sentinel Event Database or through the hospital's own risk management experience.

Finally, the standards make clear the hospital's responsibility to tell a patient if he or she has been harmed by the care provided.

With the implementation of these standards — which became effective as of July 1, more than 50% of all of the Joint Commission's hospital standards relate directly to patient safety. To learn more about the patient safety standards, visit the web site http://www.jcaho.org/ptsafety_frm.html ▼

ASHP offers on-line oncology review course

The American Society of Health-System Pharmacists (ASHP) in Bethesda, MD, is offering an on-line tool to help pharmacists prepare for the Board of Pharmaceutical Specialties certification examination in oncology pharmacy.

The review course provides users a concentrated update on the diseases, therapies, regulatory issues, pharmacology, and statistics important to oncology pharmacy practice. Participants will hear an audio presentation and view accompanying slides for up to 19 course modules. After viewing the presentation, pharmacists can complete the tests on-line and receive their grade and certificate immediately.

Users can purchase individual modules or the complete course. Access to an individual module is available for eight weeks; purchasers of the full course will have access to the materials for six months. For fee and other information, visit the web site http://www.ashp.org/oncology. ■

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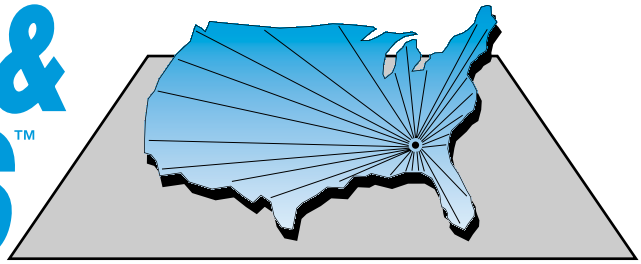

Formulary evaluation of direct thrombin inhibitors

By **Michelle Newman**, PharmD*

Mechanism of action

Argatroban and lepirudin are direct thrombin inhibitors. Argatroban reversibly binds to the catalytic site of thrombin. It also is capable of inhibiting the action of both free and clot-association thrombin. Lepirudin binds irreversibly to both the catalytic and substrate-recognition sites of thrombin. Both argatroban and lepirudin lack any structural homology with heparin and do not cross-react with heparin. Danaparoid is a heparinoid that acts by antithrombin-mediated inhibition of Xa and IIa. It is associated with cross-reactivity with unfractionated heparin (UFH) for heparin-induced thrombocytopenia (HIT) antibodies.

Indications

Argatroban and lepirudin are indicated for treatment of thrombosis in patients with HIT. Argatroban also is approved for prophylaxis of thrombosis in this population. Danaparoid is indicated for prophylaxis of postoperative deep vein thrombosis (DVT) and in patients undergoing elective hip replacement surgery. It is not approved for patients with HIT, but has been used for this purpose.

Pharmacokinetics

The pharmacokinetics of argatroban, lipirudin, and danaparoid are summarized in **Table 1, opposite**.

Dosing

The recommended initial dose for argatroban is 2 mcg / kg / min, administered as a continuous infusion. aPTT should be monitored two hours after initiating therapy. Dosing adjustments may be required to attain the target aPTT: 1.5-3.0 times the initial baseline value (not to exceed 100 seconds). The dose of argatroban should not exceed 10 mcg / kg / min. Dosage adjustment is required in patients with hepatic impairment. For patients with moderate hepatic impairment, the initial dose should be 0.5 mcg / kg / min. The aPTT should be monitored closely, and the dosage should be adjusted as indicated. No dosage adjustment is necessary for renal impairment.

The recommended initial dose for lepirudin is a bolus of 0.4 mg / kg followed by 0.15 mg / kg / hr (up to 110 kg) infusion. The dose should be titrated to achieve an aPTT of 1.5-2.5 times the initial baseline. Monitoring of aPTT should be done four hours after start of lepirudin infusion and at least once daily thereafter. A dosage adjustment is recommended in patients with a serum creatinine greater than 1.5 mg / dL. No dosage adjustment is necessary for patients with hepatic impairment.

Danaparoid is administered subcutaneously or intravenously. Therapeutic doses of danaparoid reported in the literature vary, generally ranging from 2,000 units to 4,500 units per 24 hours, usually divided into two or three daily doses. Specific recommendations for dosage reduction have not been established for danaparoid, but caution is recommended by the manufacturer for patients with serum creatinine of 2 mg / dL or greater. At present, modest dosage reductions should be considered in those patients with a creatinine clearance of less than 20. Antifactor Xa

Table 1. Pharmacokinetics

Variable	Argatroban	Lepirudin	Danaparoid
Half-life	39-51 min	1.3 hr	24 hr
Elimination	Hepatic	Renal	Renal
Monitoring	aPTT	aPTT	Anti-Xa assay

levels should be monitored in patients with renal failure and in patients who weigh less than 60 kg or greater than 90 kg who are taking danaparoid. Because Antifactor Xa levels may take several days to obtain, they may not be practical for use in short-term therapy.

Contraindications

Argatroban is contraindicated in patients with overt major bleeds or in patients hypersensitive to the product or its components. Lepirudin is contraindicated in patients who are hypersensitive to hirudins. Danaparoid is contraindicated in severe hemorrhagic diathesis (e.g., hemophilia, idiopathic thrombocytopenic purpura); active major bleeding state, including hemorrhagic stroke in the acute phase; and hypersensitivity to danaparoid or pork products.

Warnings/precautions

Warnings and precautions are similar with the three drugs. The warnings for argatroban include hemorrhage that can occur at any site in the body and the discontinuation of all parenteral anticoagulants before administration of argatroban. Precautions include administering argatroban to patients with hepatic disease and concomitant use with warfarin, which may result in a prolonged international normalizing ratio (INR).

Lepirudin's warnings include carefully assessing the risk of administration vs. its anticipated benefit in patients with an increased risk of bleeding, and use in patients with renal function impairment. Roughly 40% of patients develop antihirudin antibodies that may lead to an increase in anticoagulant effects. Hepatic injury (cirrhosis) also may lead to an increase in anticoagulant effects. Like argatroban, when used concomitantly with warfarin, lepirudin results in a prolonged INR.

While taking danaparoid, cross-reactivity with UFH can occur with antiplatelet antibodies in patients with HIT. Patients who are sulfite-sensitive may experience an allergic-type reaction, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes while taking danaparoid. It is recommended that complete blood counts, including a platelet count and a stool occult blood test be done periodically while on danaparoid, lepirudin, and argatroban to monitor for bleeding and platelet count recovery.

Adverse reactions

Excessive bleeding has been reported in up to 45% of patients treated with danaparoid for thromboembolism prophylaxis, with major hemorrhagic episodes (including GI bleeding and wound hematoma) occurring in up to 6% of patients.

The adverse events reported for argatroban and lepirudin cannot be directly compared, as these events were evaluated in separately controlled clinical trials. Argatroban's hemorrhagic events were divided into major and minor events. **(See Table 2, p. 3.)** With the current information available, it is unknown if either drug causes fewer hemorrhagic events with the recommended doses. Nonhemorrhagic adverse events associated with argatroban, lepirudin, and danaparoid are listed in **Table 3, p. 4.**

Drug interactions

Argatroban, lepirudin, and danaparoid may interact with other anticoagulants, antiplatelet drugs, and thrombolytics by increasing the risk of bleeding. Intracranial bleeding occurred in 1% of patients receiving argatroban and 0.6% of patients receiving lepirudin concomitantly with thrombolytics. Warfarin may prolong the INR with argatroban and lepirudin.

Conversion to oral therapy

The manufacturers of lepirudin and argatroban have provided guidelines for switching to oral therapy. To switch to oral therapy (such as warfarin) from lepirudin, gradually reduce the dose of lepirudin to achieve an aPTT ratio of 1.5 before initiating oral therapy. As soon as an INR of 2 is reached on combined therapy, lepirudin therapy should be discontinued. When initiating oral therapy on argatroban, the infusion of argatroban should be $\leq$ 2 mcg / kg / min. Once the INR is > 4 on combined therapy, discontinue argatroban. Repeat an INR in 4-6 hours. If the INR is below the desired therapeutic range, resume the argatroban infusion and repeat the procedure daily until the desired range is achieved.

Clinical trials

The safety and efficacy of argatroban has been evaluated in two prospective, open-label, historically controlled studies. These studies were similar in design, objectives, and treatment options. Both studies included males and nonpregnant females 18-80 years of age with a clinical diagnosis of HIT with or without thrombosis. Patients with a documented unexplained aPTT > 200% control, coagulation disorder, or bleeding diathesis; lumbar puncture within the last seven

Table 2. Hemorrhagic adverse reactions

Adverse reaction	Argatroban % (control) n = 568 (n = 193) **Major events**	Argatroban % (control) n = 568 (n = 193) **Minor events**	Lepirudin % (control) n = 113 (n = 91) **Total events**
GI	2.3 (1.6)	14.4 (18.1)	5.3 (6.6)
Genitourinary and hematuria	0.9 (0.5)	11.6 (0.8)	4.4 (0)
Decreased Hbg/Hct	0.7 (0)	10.4 (0)	12.4 (1.1)
Multisystem hemorrhage and DIC	0.5 (1)	N/A	N/A
Limb and below-the-knee amputation stump	0.5 (0)	N/A	N/A
Intracranial hemorrhage	0 (0.5)	N/A	0 (2.2)
Bleeding from puncture sites and wounds	N/A	N/A	10.6 (4.4)
Other hematoma and unclassified bleeding	N/A	N/A	12.4 (1.1)
Epistaxis	N/A	N/A	4.4 (1.1)
Hemothorax	N/A	N/A	0 (1.1)
Vaginal bleeding	N/A	N/A	1.8 (0)

days; or a history of previous aneurysm, hemorrhagic stroke, or recent thrombotic stroke within the past six months were excluded from these studies.

The initial dose of argatroban given in each study was 2 mcg/kg/min as a continuous infusion. Dosage adjustments were made to achieve an aPTT of 1.5-3.0 times the baseline. The primary efficacy analysis was based on a comparison of event rates for a composite endpoint that included death (all causes), amputations (all causes), or new thrombosis during the treatment or follow-up period of 37 days. The secondary endpoints were the evaluation of the event rates for the components of the composite endpoint and the time to event.

The first study enrolled 304 patients to receive argatroban and retrospectively evaluated 193 patients for historical controls. The result for the composite endpoint of argatroban is 34.2% vs. 43.0% for the control group. The author stated it was a significant improvement; however, no P values were given. The time to first event also was increased in the argatroban group. The second study showed similar results with fewer of the composite endpoints and an increased time to first event for argatroban. These studies currently have not been published, and evaluation of statistical significance is not available for study endpoints.

Lepirudin also was evaluated in two prospective, open-label, historically controlled trials that were similar in study design. These studies included patients who were 18 years old or older with a diagnosis of HIT based on clinical criteria and presence of HIT antibodies. The patient also must have had a definite need for parenteral antithrombotic therapy or prophylaxis. The studies excluded patients who required hemodialysis or hemofiltration; were anticipated to comply poorly; had known hypersensitivity to r-hirudin; or were pregnant. The efficacy was based on the comparison of combined and individual incidences of death, amputations, new thromboembolic complications, and incidences of bleeding with the lepirudin group and the control group. Patients in the lepirudin group were on average seven years younger and had more multiple thromboembolic complications at baseline. The results of the combined endpoints at day 35 were reduced significantly (P = 0.014) for the lepirudin group vs. the control group (9.9% vs. 23.0%). Bleeding rates were similar in both groups.

In the second study, fewer of the lepirudin-treated patients experienced an event at day 35, but it was not statistically significant. Bleeding events occurred statistically more often in the lepirudin group than the control group (P = 0.0001). These bleeding events were minor, not requiring transfusion and no intracranial bleeds were

observed. Limitations for historical controlled studies include an increased risk of bias in the selection of the control patients, and missing data may have a large effect on the study results. These studies were also not blinded or randomized due to ethical reasons.

Danaparoid has not been extensively studied for the treatment of HIT, even though it is commonly used. A retrospective review of 42 patients with acute or past HIT included patients with a likely diagnosis of HIT based on several criteria. Criteria included a decrease in platelet count by 50% from baseline, interval of HIT onset > 5 days in cases of initial exposure or interval of < 4 days in cases of re-exposure, normalization of platelet count within 10 days after cessation of heparin therapy, and a thromboembolic complication during heparin therapy. Patients received 600-800 units every 12 hours either after nonvascular surgery or in medical situations, and 100-300 units / hr infusion post cardiac surgery for prevention of venous thromboembolic complications. For treatment of acute thromboembolism complications, a step-down infusion rate was advised: 400 units / hr for 4 hours, 300 units / hr for 4 hours, and then the maintenance infusion rate of 100-370 units / hr. Twenty-six patients were treated for acute HIT. In this group, no new thrombotic complications developed while on danaparoid; however, danaparoid failed to treat a thrombotic complication of HIT in two patients (7.6%), and three patients experienced bleeding complications, one minor and two major events. At the one-month follow-up after the withdrawal of danaparoid, no thrombosis had recurred.

In the prophylaxis group, 16 patients were treated for 20 events and no thrombotic

Table 3. Nonhemorrhagic adverse reactions

Adverse reaction	Argatroban % (control) n = 568 (n = 193)	Lepirudin % (control) n = 113 (n = 91)	Danaparoid % (placebo) n = 645 (n = 135)
Dyspnea	8.1 (8.8)	N/A	N/A
Hypotension	7.2 (2.6)	N/A	N/A
Fever	6.9 (2.1)	5.3 (0)	22.2 (0.7)
Diarrhea	6.2 (1.6)	N/A	N/A
Sepsis	6 (12.4)	3.5 (5.5)	N/A
Cardiac arrest	5.8 (3.1)	N/A	N/A
Nausea	4.8 (0.5)	N/A	14.3 (2.2)
Ventricular tachycardia	4.8 (3.1)	0 (0)	N/A
Pain	4.6 (3.1)	N/A	7.6 (3)
UTI	4.6 (5.2)	N/A	2.6 (0.7)
Vomiting	4.2 (5.2)	N/A	2.9 (2.2)
Infection	3.7 (3.6)	1.8 (1.1)	N/A
Pneumonia	3.3 (9.3)	4.4 (5.5)	N/A
Atrial fibrillation	3 (11.4)	N/A	N/A
Coughing	2.8 (1.6)	N/A	N/A
Abnormal renal function	2.8 (4.7)	1.8 (4.4)	N/A
Abdominal pain	2.6 (1.6)	N/A	N/A
Cerebrovascular disorder	2.3 (4.1)	N/A	N/A
Abnormal liver function	N/A	5.3 (0)	N/A
Allergic skin reactions	N/A	3.5 (5.5)	4.8 (0)
Heart failure	N/A	1.8 (2.2)	N/A
Multiorgan failure	N/A	3.5 (0)	N/A
Pericardial effusion	N/A	0 (1.1)	N/A
Insomnia	N/A	N/A	3.1 (0)
Headache	N/A	N/A	2.6 (0.7)
Dizziness	N/A	N/A	2.3 (0)
Constipation	N/A	N/A	11.3 (0)
Peripheral edema	N/A	N/A	3.3 (0)
Joint disorder	N/A	N/A	2.6 (0)

complication occurred during the danaparoid treatment period. One minor hemorrhagic event occurred during the treatment period and one recurrence of DVT occurred during the one-month follow-up. Overall, the mean time of platelet count recovery was six days. The overall mortality was eight of 42 patients (19%), and the mortality caused by thromboembolic complications was two of 42 patients (5%). Cross-reactivity occurred in three of 46 patients (6.5%) without thrombotic complications. The study reliability is limited because of a small sample size and a retrospective design, and statistical significance was not well assessed.

Cost

At Huntsville Hospital in Huntsville, AL, danaparoid 1,500 units Q 12 hours is less expensive than the recommended doses of argatroban or lepirudin. An average daily argatroban regimen is approximately $50 less expensive than that of lepirudin, at the surveyed hospital.

Summary

Currently, danaparoid does not appear to be the drug of choice to treat HIT for several reasons. It has a 5-10% cross-reactivity with UFH antibodies. It has a much longer half-life than lepirudin and argatroban and is more difficult to monitor. It is contraindicated in patients with hypersensitivity to pork, and it should not be given to people with sulfite allergies. The dose needs to be adjusted in renal impairment, but the manufacturer has not established guidelines. Also, guidelines are not available for transitioning to oral therapy.

Argatroban and lepirudin are similar in many ways. Neither product cross-reacts with UFH and

Table 4. Summary

	Lepirudin	Argatroban	Danaparoid
Class	Direct thrombin inhibitor	Direct thrombin inhibitor	Heparinoid
Indications	Treatment of thrombosis in patients with HIT	Treatment and prophylaxis of thrombosis in patients with HIT	Indicated for prophylaxis of post-operative DVT, in patients undergoing elective hip replacement surgery
Heparin cross-reactivity	None	None	Yes (5-10%)
Half-life	1.3 hr	39-51 min	24 hr
Elimination	Renal	Hepatic	Renal
Route of administration	IV or SC	IV	IV or SC
Monitoring	aPTT	aPTT	Antifactor Xa levels
Dosage adjustments	Renal impairment	Hepatic impairment	Renal impairment
Contraindications	Hypersensitive to hirudins	Overt major bleeds or hypersensitive to argatroban	Severe hemorrhagic diathesis; active major bleeding state; hypersensitivity to danaparoid or pork products
Protamine reversal	No	No	Minimal
Warnings/precautions	Use in patients with increased risk of bleeding and with renal function impairment. Approximately 40% of patients develop antihirudin antibodies that lead to an increase in anticoagulant effects.	Hemorrhage can occur at any site in the body. Discontinue all parenteral anticoagulants before administration. Use in hepatic disease.	Perform complete blood counts periodically. Cross-reactivity with antiplatelet antibodies with UFH can occur. Patients with sensitivity to sulfites may have an allergic-type reaction.
Potential drug interactions	Oral anticoagulants, antiplatelet agents, and thrombolytics.	Oral anticoagulants, antiplatelet agents, and thrombolytics.	Oral anticoagulants, antiplatelet agents, and thrombolytics.
Effect on PT/INR	Prolongation	Prolongation	None

both have a short half-life. The monitoring parameters, adverse events, drug interactions, product stability / compatibility, and ease of dosing and administration are similar. Argatroban can be used in patients with renal impairment because dosage adjustment is not necessary. It also should be considered as alternative therapy for patients who develop antibodies to lepirudin, which increases anticoagulation effects. Lepirudin should be considered for patients with hepatic impairment.

See **Table 4, p. 5**, for a quick reference guide and summary of all three therapies.

*(Editor's note: * written while a PharmD candidate at McWhorter School of Pharmacy, Samford University, Birmingham, AL.)*

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IN THE PIPELINE

• Novogen Limited announced the start of the first trial in the United States for phenoxodiol, which targets multiple enzymes that are common to many human cancers. The patients enrolled in the Cleveland Clinic Foundation trial have **late-stage, metastatic cancers** of any type other than breast cancer.

• Versicor announced the start of a Phase II clinical study to evaluate the efficacy and safety of its investigational antibiotic, dalbavancin (formerly V-Glycopeptide), for the treatment of **complicated skin and soft-tissue infections** caused by gram-positive bacteria, usually *Staphylococci*. This randomized, controlled, open-label study will enroll about 60 hospitalized patients with skin and soft-tissue infections.

• Matritech announced that it has begun patient recruitment for a multi-center clinical study of its NMP66 blood test for the early detection of **breast cancer**. The clinical study, which will be conducted at six medical centers around the country, will enroll approximately 1,000 patients.

• Millennium Pharmaceuticals announced the initiation of a Phase II clinical trial of LDP-341 (also known as PS-341) for patients with **chronic lymphocytic leukemia** (CLL). This clinical trial, the third Phase II study of LDP-341 as a single agent in hematologic malignancies, is an open-label dose-finding study of LDP-341 in patients with CLL who have relapsed during or within six months of receiving treatment with a purine analog. The goal of this study is to assess the safety and response rate associated with two doses of LDP-341 in patients with B- or T-cell CLL.

• Following a meeting with the Food and Drug Administration, Antisoma plc announced its intention to extend recruitment to the Phase III SMART study of pemtumomab (formerly known as Theragyn) in the treatment of **ovarian cancer**. The SMART study is designed to confirm that treatment of certain ovarian cancer patients with Yttrium-90 radiolabeled pemtumomab, in

addition to standard care, demonstrates a statistically significant survival benefit over standard care alone. Recruitment has reached the initial target of 300 patients.

• Guilford Pharmaceuticals announced that the FDA has accepted for review its supplemental New Drug Application to expand the labeled indication for polifeprosan 20 with carmustine implant (Gliadel Wafer) to include first-line therapy in patients newly diagnosed with **malignant glioma.**

• Viragen announced the commencement of pre-clinical studies to evaluate a monoclonal antibody for the treatment of many **cancers**. The studies are being conducted in collaboration with the National Institutes of Health in Bethesda, MD.

• SuperGen announced that is has completed patient enrollment for its second of three Phase III clinical studies of rubitecan, its oral chemotherapy compound in development for the treatment of **pancreatic cancer**. This study, which has enrolled more than 400 patients at 200 medical centers across the United States, compares rubitecan to the most appropriate chemotherapy as third-line therapy for patients who previously have failed multiple types of chemotherapy.

• Millennium Pharmaceuticals announced that a Phase II clinical trial has been initiated with LDP-977. The multicenter trial is a randomized, placebo-controlled, double-blind, parallel group, dose-finding study to evaluate the safety and effectiveness of LDP-977 in adult patients with **chronic asthma**.

• Versicor announced the start of a Phase II clinical study to evaluate anidulafungin (formerly referred to as V-Echinocandin) for the treatment of **invasive candidiasis/candidemia**. This randomized open-label study will enroll about 20 hospitalized patients in the United States with a documented diagnosis of candidiasis/candidemia. Patients will be examined for clinical and microbiological responses at the conclusion of therapy and two weeks following therapy.

• EntreMed announced a collaborative relationship with Aventis Pharmaceuticals for Phase II clinical studies in patients with **hormone-refractory prostate cancer**. The objectives of this initial study are to assess safety, dose finding, and tolerability of daily oral angiogenesis inhibitor (Panzam) in combination with weekly docetaxel (Taxotere) in prostate cancer patients and to measure PSA levels and tumor responses following Panzem/Taxotere combination treatment.

• Cellegy Pharmaceuticals announced that it filed a new drug application with the FDA requesting review of existing data on its product, nitroglycerin ointment (Anogesic), for the treatment of pain associated with **chronic anal fissures**. The company also announced that it has completed patient enrollment in its ongoing second Phase III anal fissure pain study.

• NeoTherapeutics announced that it has expanded its Neotrofin **spinal cord injury** trial to include Gaylord Hospital in Wallingford, CT. Gaylord Hospital, which is affiliated with Yale University and the University of Connecticut, is the second site participating in the 12-week, open-label study. Additional sites are expected to join the study over the next couple of months. ■

New FDA Approvals

• *Antiepileptic oral suspension oxcarbazepine (Trileptal) by Novartis Pharmaceuticals Corp.* The Food and Drug Administration (FDA) has granted marketing clearance for an oral suspension formulation of Trileptal in the treatment of people with **epilepsy** who have difficulty taking tablets. Trileptal is available as a 300 mg/5 mL (60 mg/mL) oral suspension.

• *Travoprost ophthalmic solution (Travatan) by Alcon Universal.* Travatan has been approved by the FDA for the reduction of elevated intraocular pressure (IOP) in patients with **open-angle glaucoma or ocular hypertension**. It is indicated for patients who are intolerant of or insufficiently

responsive to other intraocular pressure-lowering medications. The recommended dosage is one drop in the affected eye(s) once daily in the evening.

• *Campath, a humanized monoclonal antibody, by Berlex Laboratories.* The FDA has granted accelerated approval for Campath as an injectable treatment for **B-cell chronic lymphocytic leukemia** (B-CLL). Campath is designed for use in B-CLL patients who have been treated with alkylating agents and have failed fludarabine therapy.

• *Albuterol sulfate inhalation aerosol (Ventolin HFA) by GlaxoSmithKline.* The FDA has approved Ventolin HFA for the treatment or prevention of **bronchospasm in adults and children four years of age and older** with reversible obstructive airway disease, and for the prevention of exercise-induced bronchospasm in patients four years of age and older. Ventolin HFA is a new version of the Ventolin metered-dose inhaler (MDI) currently marketed by GlaxoSmithKline. Unlike the current version, however, the new inhaler does not use chlorofluorocarbons (CFCs) to propel the medication. Ventolin HFA uses an alternative propellant called HFA or hydrofluoroalkane.

• *Azelaic acid cream 20% (Finevin) by Berlex Laboratories.* The FDA has approved the marketing of Finevin for the topical treatment of mild to moderate inflammatory **acne vulgaris**. Finevin should be applied twice a day, in the morning and evening. A majority of patients with inflammatory lesions may experience an improvement in their acne within four weeks of beginning treatment. However, treatment may be continued over several months, if necessary.

• *Calcium acetate (PhosLo) capsules and gelcaps by Braintree Laboratories.* PhosLo has been approved for the control of hyperphosphatemia in end-stage renal failure in adult patients. Excessive dosage of PhosLo induces hypercalcemia; therefore, early in the treatment during dosage adjustment serum calcium should be determined twice weekly. The serum calcium times phosphate (CaXP) product should not be allowed to exceed 66. ■

Heparin can put patients at risk for HIT

Heparin, a common anticoagulant used to prevent blood clots, is one of the most commonly used medications in U.S. hospitals. However, heparin therapy can cause an immune-disorder known as heparin-induced thrombocytopenia (HIT).

Each year, nearly 12 million Americans are treated with heparin for conditions such as blood clots in the legs or lungs, heart attacks, or angioplasty. Of these 12 million people, as many as 360,000 will develop HIT, an estimated 120,000 will develop a thrombotic complication (stroke, limb amputation or death), and up to 36,000 will die.

HIT is diagnosed clinically by a drop in blood platelet count below 100,000/microliter or a dramatic 50% reduction in platelet count, as compared to baseline. Although heparin is administered to prevent blood clots, in HIT patients, it paradoxically may result in the development of blood clots.

HIT usually occurs five to 10 days following heparin treatment, although it may begin sooner. Diagnosis of the disorder can be complicated by similarities between the symptoms of HIT and other syndromes, as well as the limitations of existing laboratory assays. Diagnosis can be made even more challenging because physicians expect bleeding, not clotting, with thrombocytopenia. Thus, physicians inadvertently may exacerbate the condition by continuing anticoagulation therapy with heparin in patients who develop HIT.

If left untreated or misdiagnosed, HIT patients may develop serious complications such as pulmonary embolism, heart attack, limb damage requiring amputation, or even death. Mortality from HIT is estimated to be as high as 30% in patients who develop serious complications. ■

From the editor: Call for drug reviews

If you or your institution has a drug review (similar to those published in *Drug Criteria & Outcomes*) that *Drug Utilization Review* readers would find helpful in clinical practice, please contact Sue Coons at: spcoons@aol.com. ■