AMERICAN HEALTH CONSULTANTS

DRUG UTILIZATION REVIEW

Pharmaceutical Care Across the Continuum

IN THIS ISSUE

JANUARY 2002

VOL. 18, NO. 1 (pages 1-8)

Blockbuster sepsis drug drotrecogin alfa (activated) receives FDA approval

Pharmacists share concerns about cost, appropriate use

The Food and Drug Administration (FDA) has approved the first biologic treatment for the most serious forms of sepsis, a life-threatening illness caused by severe infection. The price tag for drotrecogin alfa (activated) (Xigris) is high, however, and some pharmacists wonder if the risk factors are steep, too.

"[The drug] may hold some benefit in a certain subgroup of septic patients," says **Daniel Albrant**, PharmD, president of Pharmacy Dynamics, a health care consulting business based in Arlington, VA. "But it's always going to have a significant downside with a bleeding risk and maybe some other things we don't know about yet. It's not going to cure sepsis."

Drotrecogin alfa (activated) is a genetically engineered version of naturally occurring human protein C, which interferes with some of the body's harmful responses to severe infection. The drug is indicated for patients with severe sepsis (sepsis associated with severe organ dysfunction) who have a high risk of death.

FDA approval was based on results from the Phase III PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial. In the trial, researchers studied 1,690 sepsis patients, giving half of the participants the drug and the other half a placebo. Results showed a 6% reduction in the overall mortality rate, from 31% to 25%, during the 28-day study period. Among patients who had higher risks of dying, mortality was reduced by 13%. Drotrecogin alfa (activated) did not lower mortality rates in study patients who were less severely ill.

Following approval of the drug, Dept. of Health and Human Services Secretary Tommy Thompson issued an unusual statement praising the FDA's decision. "Today's approval of the new weapon against sepsis, called Xigris, is a hopeful milestone because this product is designed to actually interrupt the body's harmful responses to severe infection." He went on to "congratulate the researchers whose long efforts have yielded Xigris," and he commended the FDA for its "careful work in reviewing the monitoring of this new product."

Approval of drotrecogin alfa (activated), however, was not a guarantee for Indianapolis-based drug manufacturer Eli Lilly. On Oct. 16, the FDA's Anti-Infective Drugs Advisory Committee voted not to recommend the drug's approval based on information that indicated the drug was not as safe or effective as previously thought. Some reports say that 10 of 20 panel members voted against the drug. The majority of the panel members suggested that Eli Lilly conduct additional tests on drotrecogin alfa (activated).

Possible side effect: Bleeding

Instead, the FDA voted to approve the drug for a subgroup of sepsis patients, while warning of the possible side effect of bleeding. During the time when the drug was infused in the trial (continuously over four days), serious bleeding episodes occurred in 2.4% of patients treated with drotrecogin alfa (activated) compared to 1% of patients in the placebo group. The drug is contraindicated for patients who have active internal bleeding, or who are more likely to bleed because of certain medical conditions, including recent strokes, recent head or spinal surgery, or severe head trauma.

Ten panel members said they didn't think this drug has enough scientific evidence to be approved, Albrant says. "That has to be taken into account even though the FDA gave the go-ahead. There isn't any other agent that we have for severe sepsis — each individual institution must decide whether it [the drug] is going to make a significant impact."

Albrant doesn't believe that any single agent is going to make a big difference in the multifactorial problems associated with sepsis. "We don't really understand a lot of what goes on in sepsis. Now we have a compound that we are going to throw at these folks. We don't know if this is the right dose. We don't know if this is the right duration."

One study — basically 850 patients — is not a lot to go on, he continues. "It's hard to make a decision on this drug given the fact that we have so many unanswered questions."

It's likely that Xigris will make some small benefit, he adds, but drugs coming out of research trials never perform as well as they do in clinical practice because of the vagaries of how they are used and patient idiosyncrasies. He also is concerned about the bleeding risk. "The bleeding was almost statistically significant in that small population. If you look at the contraindications of the drug, they are all bleeding issues."

If people start to bleed dramatically, there is no antidote, he says. "We start using precious resources like blood and blood products that carry their own risks." Plus, some patients may end up spending more days in the intensive care unit (ICU). "At $1,500 a day for the cost of an ICU bed, you eat up a lot of dollars."

Albrant is urging his clients to be cautious with the drug. Physicians, however, are telling him that it would be hard not to use it. If they wait, they might become vulnerable to lawyers who argue, "You had this drug available, why didn't you use it?"

Albrant counters by saying that drotrecogin alfa (activated) isn't a standard of care at this point. From a tort standpoint, lawyers usually look at what is the standard of care, he says. "In this case, it is still mechanical ventilation, fluids, antibiotics, and agents for blood pressure. I don't think anyone can argue that it is a standard of care yet. There is no clinical experience with it."

The budget eater

Even if health systems are eager to use drotrecogin alfa (activated), they have to find a way to pay its hefty price tag. The average net wholesale price is $6,800 per 96-hour course of therapy.

An average-size hospital can see 100 septic patients a year. That is beyond a challenge to budget, Albrant says. "There is no way to budget for a drug that is going to cost somewhere between a half-million dollars to $1 million in the average pharmacy budget. As a percentage,

COMING IN FUTURE MONTHS

- A look at automated dispensing machines vs. pharmacist shortage
- The problem of fake drugs
- Are placebo controls ethical?
- A cost-cutting success story
- Drug company mergers squeeze drug availability

a single drug that is going to eat up 20%-25% of an average pharmacy budget is unheard of."

He suggests treating the drug as a capital expenditure and not as a pharmacy addition. "People who are making financial decisions for the institution need to understand the impact of adding this drug to the formulary." These decision-makers also need to decide if they can afford to add the drug while they learn if any other morbidities are associated with it.

New cost of doing business

Although the drug is considered very expensive, at least one health system's chief financial officer considers drotrecogin alfa (activated) a new cost of doing business. "Our guiding principal will be, 'Based on clinical criteria, does the patient need this drug?' more than 'Look how expensive this drug is, can we [afford to] use it?'" says **Steve Dedrick**, MS, director of pharmacy at Duke Medical Center in Durham, NC. "We are going to keep it patient-focused and criteria-focused, and we are going to sensitize everyone to the cost, but [the cost] is not going to be the No. 1 knee-jerk reaction."

How can we learn more?

Dedrick wishes that some sort of central database existed where health care professionals could report their individual experiences with drotrecogin alfa (activated). "It would be nice to be able to report conditions and outcomes of patients who receive the drug. We'd get smarter sooner in aggregate rather than one hospital trying to figure it out for itself."

Albrant would like the drug to undergo more trials that examine some of the issues outstanding from the PROWESS trial. Eli Lilly already has agreed to do more research. As part of its Phase IV commitments, Lilly will work with the FDA to institute post-approval trials that will include a study of the efficacy of the drug in adult patients with severe sepsis who have a lower risk of death. Eli Lilly also plans to follow up on its PROWESS patients for up to one year. ■

Health systems establish rigid guidelines for Xigris

One hospital closely followed PROWESS trial inclusion criteria

The questions about cost and appropriate use of drotrecogin alfa (activated) (Xigris) for the treatment of patients with severe sepsis who have a high risk of death have resulted in health systems establishing rigid guidelines for its use.

Duke Medical Center in Durham, NC, established a rigorous process for developing usage guidelines that involved its intensive care practicing physicians and pharmacists. "That's been a six-month process — working on where we would like this drug to be used and who can prescribe it," says **Steve Dedrick**, MS, director of pharmacy.

Duke has created an ordering form that guides the prescribers through a checklist of clinical issues. "We think that if physicians follow that guideline check-off sheet, they automatically self-select their patient based on the way the questions are answered," he says. At the end, the form tells the prescribers if they get the drug or not.

"We're trying to make sure that everyone understands that this is not a drug without some risk," Dedrick says. Physicians who are not aware of these risks would learn about them after reading that part of the check-off form. "If certain conditions are present, these patients would be selected out based on their risk factors. We see that as an easier process than having some sort of phone call approval."

Duke also will include documentation in the medical record that says the physicians thought about the issues and said "yes" or "no" on the risk criteria.

A look at one hospital's guidelines

Another hospital chose to model its guidelines **(shown on p. 4)** on the drug's Phase III PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial. For example, the hospital adopted the trial's inclusion criteria almost verbatim. The hospital also restricted usage of the drug to pulmonary critical care, surgical intensive care unit consult service, and infectious disease senior staff physicians only. ■

Guidelines for drotrecogin alfa (activated) — Xigris

Indication: Severe sepsis as demonstrated by the following:

Patient has known or suspected infection.

Such as white blood cell counts in a normally sterile body fluid, perforated viscus, chest x-ray consistent with pneumonia, and production of purulent sputum.

AND

Patient has three of the four sytemic infection response syndrome criteria:

- Body temperature ≥ 38º C (100.4º F) or ≤ 36º C (96.8º F);
- Heart rate ≥ 90 beats/min except in patients with a medical condition known to increase heart rate or those receiving treatment that would prevent tachycardia;
- Respiratory rate ≥ 20 breaths/min or a $PaCO_2$ ≤ 32 mmHg or mechanical ventilation; and
- White blood cell count of ≥ 12,000/mm^3 or ≤ 4,000/mm^3 or > 10% bands.

AND

Evidence of at least one of the following signs of organ dysfunction due to sepsis that has been present for no longer than **24 hours**:

- **Cardiovascular**

An arterial systolic blood pressure ≤ 90 mmHg or a mean arterial blood pressure (MAP) ≤ 70 mmHg for at least one hour despite adequate fluid resuscitation, adequate intravascular volume status, or the need for vasopressors to maintain systolic blood pressure ≥ 90 mmHg or MAP ≥ 70 mmHg.

- **Renal**

Urine output < 0.5 mL/kg/hr for one hour despite adequate fluid resuscitation.

- **Respiratory**

PaO_2/FiO_2 ≤ 250 in the presence of other dysfunctional organs or ≤ 200 if lung is only dysfunctional organ.

- **Hematology**

Platelet count of < 80,000/mm^3 or a 50% decrease in the platelet count over the previous three days.

- **Metabolic acidosis**

pH ≤ 7.3 or base deficit ≥ 5 mmol/L with a lactate level > 1.5 times the upper limit of normal.

Situations in which drotrecogin alfa (activated) is not indicated:

- Mild-to-moderate sepsis without evidence of end-organ dysfunction;
- Moribund patients in whom death is imminent; and
- Patients whose families or physician is not committed to the aggressive management of their underlying medical condition, i.e., do-not-resuscitate status.

Contraindications: *(final criteria pending approval of product labeling)*

- Pregnancy or breast feeding;
- Age < 18 years;
- Weight > 135 kg;
- Platelet count < 30,000/mm^3;
- Active bleeding at any site;
- Recent surgery or trauma with uncertain hemostasis;
- Known hypercoagulable condition;
- Recent (within three months) deep vein thrombosis or pulmonary embolism;
- Severe head trauma, intracranial or spinal surgery, or stroke within three months;
- History of bone marrow, kidney, small bowel, liver, lung, or pancreas transplantation;
- Human immunodeficiency virus infection in association with a last known CD4 count of ≤ 50/mm^3;
- Chronic renal failure requiring hemodialysis or peritoneal dialysis (acute renal failure is not a contraindication);
- Known or suspected portosystemic hypertension, chronic jaundice, cirrhosis, or chronic ascites;
- Acute pancreatitis with no established source of infection.

Use any of the following medications or treatment regimens:

- Unfractionated heparin to treat an active thrombotic event within eight hours (prophylactic heparin ≤ 15,000 units/d permitted);
- Low molecular weight heparin at a higher dose than recommended for prophylactic use within 12 hours;
- Warfarin use within seven days;
- Aspirin use > 650 mg/d within three days;
- Thrombolytic use within three days (catheter clearance use is permitted);
- Glycoprotein IIb/IIIa antagonists within seven days;
- Antithrombin III at a dose > 10,000 units within 12 hours.

Dosing:

Pending approval of final labeling, 24 mcg/kg/hr is infused for 96 hours. The infusion is stopped one hour before any percutaneous procedure or major surgery and resumed one hour or 12 hours later, respectively, in the absence of bleeding complications.

Numbers to treat:

- To save one life: 16;
- To have one serious bleeding complication: 66.

Cost:

The current estimate is $5,000-$7,000 for an average course of treatment. ■

Feds revising drug discount proposal

Outpatient drug reimbursement also targeted

The Bush administration is once again preparing to offer discounts on medicines sold to Medicare beneficiaries, even though an injunction on its original plan still is in place.

In late November, administration officials told the *New York Times* (*NYT*) that the president would formally propose a new plan in the next several weeks. "We are just trying to get seniors cheaper prices," **Thomas A. Scully**, administrator of the Centers for Medicare and Medicaid Services (CMS), told the newspaper.

The original plan was blocked in September by a federal district court judge, who said the president "acted without legal authority" and did not provide proper notice and an opportunity for public comment on the plan.

Scully told the *NYT* that the new proposal "has a little more structure to it and is much more detailed" than the original plan. He said the administration also would seek public comment on it. The statutory authority of the plan, however, still is in question.

There are many opinions as to when this plan might be released, says **Susan C. Winckler**, RPh, Esq., group director of policy and advocacy for the American Pharmaceutical Association (APhA) in Washington, DC. "Some say it is ready to go; others say it is not. We're just watching every day."

The administration's desire to use "market forces" to get lower prices continues to be a concern, she says. "Does that mean that they would be securing mandatory rebates from manufacturers or mandatory rebates from community pharmacies? And who would be securing those rebates?"

Fixing 'flaws' in outpatient drug payments

Bush administration officials are not the only ones looking at drug prices. The House Committee on Energy and Commerce is considering changing the current reimbursement system for outpatient drugs covered by Medicare, too.

Committee Chairman **W.J. "Billy" Tauzin** has written a letter to CMS Administrator Scully outlining a plan to replace the pricing structure from one based on a drug's average wholesale price (AWP) to one that relies on an "average sales price" (ASP). Tauzin is concerned that drug manufacturers use the AWPs to dramatically inflate the payments made for drugs by Medicare and Medicaid beneficiaries.

Tauzin says the ASP will be clearly defined and will include manufacturer-provided rebates, chargebacks, and other discounts to purchasers.

Although Winckler agrees that some change from the AWP structure needs to be made, any change has to recognize that the AWP spread has been paying for services that are required to get those medications to patients.

"If you change the formula to get a more accurate assessment of what the medication costs, that has to be accompanied by a dispensing fee or fee to cover what it takes to get the medication into the pharmacy or into the physician's office and keep it for a while," she explains. "It also needs to cover the preparation of the medication and then the services to make that medication work. You can't just change the product end of the formula without building in payment for those other services." ■

News from the ASHP Midyear Clinical Meeting

Pharmacists and counterterrorism planning

Since the Sept. 11 terrorist attacks, the American Society of Health-System Pharmacists (ASHP) in Bethesda, MD, has been evaluating the nation's emergency response to terrorism — and pharmacists' roles in that response.

On Nov. 9, the association convened an executive session on emergency preparedness that brought together more than 35 representatives from federal public health and preparedness offices, pharmaceutical manufacturers, wholesalers, group purchasing organizations, academic health science centers, community hospitals, and health organizations. The session identified significant weaknesses of the response system, including the need to include more pharmacists in emergency-response planning and to more easily deploy their services when needed.

"Drug products are central to every aspect of emergency planning, and pharmacists must be involved in ensuring that emergency plans detail how to disseminate the right medication to the right patient," says **Henri R. Manasse Jr.**, PhD,

ScD, ASHP executive vice president and chief executive officer.

At its Midyear Clinical Meeting in New Orleans in December, the ASHP issued a statement urging hospital and health-system pharmacists to exercise their responsibilities for counterterrorism, including a call for leaders of emergency planning at the federal, regional, state, and local levels to call upon pharmacists to participate in the full range of issues related to pharmaceuticals.

General principles

The statement included general principles about how pharmacists can assist in emergency planning and response:

• On the basis of their education, training, experience, and legal responsibility, pharmacists should have a key role in the planning and execution of:

(a) pharmaceutical distribution and control; and

(b) drug therapy management of patients in the event of homeland terrorist attack with weapons of mass destruction (WMD), especially chemical, biological, and nuclear agents.

• The expertise of the pharmacist must be brought to bear in:

(a) selecting pharmaceuticals and related supplies for national or regional stockpiles and local emergency inventories in counterterrorism programs;

(b) ensuring proper packaging, storage, handling, labeling, and dispensing of emergency supplies of pharmaceuticals;

(c) ensuring appropriate deployment of emergency supplies of pharmaceuticals in the event of a terrorist attack;

(d) developing guidelines for the diagnosis and treatment of victims of WMD; and

(e) ensuring appropriate education and counseling of individuals who receive pharmaceuticals from an emergency supply after a terrorist attack.

• Pharmacists must be in a position to advise public health officials on appropriate messages related to the use of essential pharmaceuticals after terrorist incidents, giving consideration to issues such as adverse effects, contraindications, effectiveness of alternative pharmaceuticals, and potential development of drug-resistant infectious agents.

• In the event of a terrorist attack, pharmacists should be called upon to collaborate with physicians and other prescribers in the drug therapy management of individual victims.

The statement also advises specific health care leadership areas: pharmacy directors, pharmacists, administrators, emergency preparedness planners, and state societies of health system pharmacists. ASHP's advice to pharmacy directors and pharmacists includes the following directives.

Advice to pharmacy directors

Every hospital and health-system pharmacy director (or designee) should:

• Become thoroughly informed of federal, regional, state, local, and institutional plans for emergency preparedness, especially as related to the distribution, control, and use of pharmaceuticals.

• Ensure that the pharmaceutical components of the institution's emergency plans are coordinated with the overall local preparedness plan involving other institutions, community pharmacies, and wholesalers, as well as coordinated with federal, regional, and state plans.

• Ensure that the appropriate pharmaceuticals and related equipment and supplies are in stock at the institution, consistent with the overall local preparedness plan, which should take into account the interim period between the occurrence of a terrorist attack and the receipt of federal or state assistance.

• Ensure that information regarding the appropriate use of pharmaceuticals in response to a terrorist attack is available to the health professionals in the institution.

• Ensure that the institution does not engage in stockpiling of pharmaceuticals without regard to local counterterrorism plans that are designed to meet the needs of the whole community.

• Ensure that pharmacy personnel are trained to implement the institution's emergency plans.

Advice to pharmacists

Every hospital and health-system pharmacist should:

• Become well informed on the threats of chemical, biological, and nuclear terrorism, including potential agents that could be used in an attack and the related diagnostic and treatment issues.

• Share with professional colleagues and patients evidence-based information on pharmaceuticals used in responding to terrorist attacks.

• Act assertively to prevent and allay panic and irrational responses after incidents of terrorism.

• Strongly discourage individuals from amassing personal stockpiles of pharmaceuticals for use in the event of chemical, biological, or nuclear terrorism.

• Consider volunteering in advance of any terrorist attack to assist in:

(a) distribution of emergency supplies of pharmaceuticals; or

(b) collaborative drug therapy management of individual victims.

- *Develop and maintain first-aid skills.*

Bioterrorism drug reference manual

The ASHP also announced that it has published a manual that gives comprehensive drug information on medications that may be needed to counter a terrorist attack.

The *AHFS DI Bioterrorism Resource Manual* contains 21 monographs drawn from *AHFS Drug Information* that provide information on the vaccines and anti-infective medications that most likely will be used to treat patients who have contracted anthrax, smallpox, or plague. The monographs include discussions of the therapeutic roles of medications such as ciprofloxacin (for treatment of anthrax), gentamicin (for treatment of plague), and smallpox vaccine. In addition, the monographs include information on:

- drug interactions, toxicity, and cautions;
- dosage and administration;
- preparations, chemistry, and stability; and
- pharmacology and pharmacokinetics.

The manual also has the most current recommendations on prevention and treatment of infectious diseases. For information, call ASHP at (301) 657-4383 or visit the web site at www.ashp.org.

Finally, the ASHP announced that it has received an educational grant from AstraZeneca in Wilmington, DE, to create a guidance manual that will assist pharmacy directors and their staffs in the establishment and operation of bioterrorism preparedness programs. The grant will support development of a book tentatively titled *Manual for Pharmacists on Bioterrorism,* which will be released this summer. ■

FDA issues stronger warnings for droperidol

The Food and Drug Administration (FDA) has strengthened the warnings and precautions sections in the labeling for droperidol, a tranquilizer used most often as a premedication for anesthesia, as treatment for nausea after anesthesia, and for sedation of agitated patients. Droperidol has been associated with fatal cardiac arrhythmias.

Specific changes to the droperidol labeling include a "black box" warning. The new warning is intended to increase the physician's focus on the potential for cardiac arrhythmias during drug administration, and to encourage the use of alternative medications for patients at high risk for cardiac arrhythmias.

Droperidol currently carries a warning about cases of sudden death at high doses (greater than 25 mg) in patients at risk for cardiac arrhythmias. Recent research has shown QT prolongation within minutes after injection of a dose of droperidol at the upper end of the labeled dose range.

In the past year, there have been reports of torsades de pointes (TdP) within or below the

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.

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), $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.)

Editorial Questions

Questions or comments? Call **Paula Cousins** at (816) 960-3730.

Editor: **Sue P. Coons**, (spcoons@aol.com).
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@ahcpub.com).
Managing Editor: **Paula Cousins**, (816) 960-3730, (paula.cousins@ahcpub.com).
Production Editor: **Caralyn Davis**.

THOMSON
AMERICAN HEALTH CONSULTANTS

currently labeled dose range. There also have been reports of sudden death or other serious cardiac adverse events.

Manufacturer Akorn Pharmaceuticals of Buffalo Grove, IL, is sending a "Dear Healthcare Professional" letter to physicians, pharmacists, and other health care professionals in the United States. The letter explains the "black box" warnings and highlights the potential for QT prolongation or TdP when this drug is administered. ▼

Postal workers see side effects from Cipro

Hundreds of postal employees who used ciprofloxacin (Cipro) for antimicrobial prophylaxis have reported adverse reactions.

More than 5,800 postal workers reported the adverse reactions in questionnaires administered to them in New Jersey, New York, and the District of Columbia 7-10 days after they received the antibiotics. The results were published in the Nov. 30 issue of the Centers for Disease Control and Prevention's M*orbidity and Mortality Weekly Report*.

Of the 3,428 people on ciprofloxacin, 666 (19%) reported severe nausea, vomiting, diarrhea, or abdominal pain; 484 (14%) reported fainting, light-headedness, or dizziness; 250 (7%) reported heartburn or acid reflux; and 216 (6%) reported rashes, hives, or itchy skin. Of those taking ciprofloxacin, 287 (8%) discontinued the medication; 116 (3%) discontinued the medication because of adverse events, 27 (1%) discontinued because of fear of possible adverse events, and 28 (1%) stopped taking the drug because they "did not think it was needed."

Only 2% of the postal employees on any medication for antimicrobial prophylaxis sought medical attention for symptoms that may have been associated with anaphylaxis.

Among the 33 people who sought medical attention for these symptoms in New Jersey and New York City, none were hospitalized and none of the symptoms were attributed to antimicrobial prophylaxis by clinicians who evaluated these people. Follow-up of postal employees in the District of Columbia who sought medical attention for symptoms that may have been associated with anaphylaxis is ongoing. ▼

Lamotrigine who?

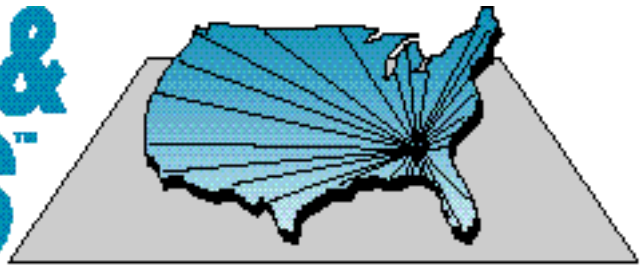
GlaxoSmithKline is continuing to receive reports about prescription dispensing errors involving its antiepileptic drug lamotrigine (Lamictal) and other medications, most commonly Lamisil, lamivudine, Ludiomil, labetalol, and Lomotil. Some epileptic patients needing Lamictal have mistakenly received other drugs; likewise, some patients prescribed other medications have erroneously received Lamictal.

London-based GlaxoSmithKline has developed materials and suggestions for pharmacists and physicians to help prevent dispensing errors. These materials include:

- a "shelf shouter" that can be used to help differentiate Lamictal from other stocked merchandise; and
- a sample of a patient-information tear sheet about Lamictal, which may be given to patients when prescriptions are filled.

For more information, contact the GlaxoSmithKline Customer Response Center at (888) 825-5249. ■

DRUG CRITERIA & OUTCOMES™



Tinzaparin formulary evaluation: DVT treatment

By **Lisa Patel**, PharmD
Auburn (AL) University*
* Written on clinical rotation at Huntsville Hospital, Huntsville, AL

The deep vein thrombosis (DVT)-related, Food and Drug Administration (FDA)-approved indications for enoxaparin (Lovenox, Aventis) include:

- prevention of DVT in patients undergoing hip replacement, knee replacement, or abdominal surgery who are at risk for thromboembolic complications;
- inpatient or outpatient treatment of acute DVT with or without pulmonary embolism when administered in conjunction with warfarin sodium;
- prevention of DVT in medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness; and
- other indications, including prevention of ischemic complications of unstable angina and myocardial infarction.

The DVT-related, FDA-approved indication for tinzaparin (Innohep, DuPont) includes:

- Treatment of DVT with or without pulmonary embolism when administered in conjunction with warfarin sodium. The safety and effectiveness of tinzaparin were established in hospitalized patients.

Mechanism of action

When binding to antithrombin III (the body's natural anticoagulant), low-molecular-weight heparin (LMWH) products cause a conformational change that increases the activity of antithrombin III. Antithrombin III can bind thrombin and prevent its effect on the coagulation system. Because less than 50% of the LMWH chains are capable of binding both antithrombin and thrombin, LMWH inhibits antifactor Xa to a greater degree than antifactor IIa. Factor Xa catalyzes the conversion of prothrombin (Factor II) to thrombin (Factor IIa). Antifactor-Xa activity correlates with antithrombotic efficacy, and antifactor IIa correlates with bleeding. Thus, LMWH products theoretically have less chance of causing bleeding than unfractionated heparins.

LMWH products also inhibit thrombin, which converts fibrinogen to fibrin (the main constituent of a thrombus). Inhibition of Factors Xa and IIa does not dissolve clots, but helps to prevent DVT and clot extension, while natural mechanisms resolve the thrombus. LMWH does not bind as extensively to plasma proteins, macrophages, or endothelial cells, resulting in a more predictable response pattern as compared to unfractionated heparin. Other actions of LMWH, of which the clinical significance has not been determined, include stimulation of endothelial cell growth factor, activation of lipoprotein lipase, suppression of aldosterone secretion, inhibition of smooth muscle cell proliferation, and induction of platelet aggregation.[1,2]

Pharmacokinetic data

LMWH products have similar molecular profiles, but structural variations create differences in biologic actions.[3,4] **(See Table 1, p. 2.)** Biological properties and extent of antifactor-Xa activity vary widely among available products. For this reason, all different LMWHs should be considered separate products. Although LMWH levels cannot be measured directly, antifactor-Xa activity, antifactor-IIa activity, and tissue factor pathway inhibitor (TFPI) can be measured as indicators of LMWH clinical activity.[5]

Depolymerization of specific LMWH products results in the loss of molecules that are greater

Table 1. Pharmacokinetic profiles

Pharmacokinetic Parameters	Tinzaparin	Enoxaparin
Average molecular weight	4,500	4,200
Half-life (hr)	3-4	3-6
Antifactor-Xa/IIa ratio	1.9	3.8
Peak (hr)*	3-5	1-5
Onset (hr)*	2-3	3-5
Duration (hr)	24	12
Area under the curve	1.35	3.47
C_{max} (IU/mL)*	0.87	0.42
Bioavailability	86.7%	92%
Preparation	Heparinase digestion	Benzylation and alkaline hydrolysis
Metabolism	Renal; Partially metabolized by desulfation and depolymerization	

* measured by antifactor-Xa plasma levels

These doses are indicated as "bridge" therapy to warfarin until a stable international normalized ratio (INR) is achieved. The 1.5 mg / kg Q24H dose of enoxaparin is indicated for inpatient therapy only.

than 18 saccharide units and molecular changes that confer varying chemical and biological profiles to each LMWH product. This smaller molecule results in a product that inhibits Factor IIa to a lesser degree compared to unfractionated heparin.[6] As stated earlier, an increase in the antifactor-Xa / IIa ratio theoretically would result in a decreased chance of bleeding. Thus, enoxaparin with an antifactor-Xa / IIa ratio of 3.9 compared to a tinzaparin value of 1.9 theoretically should result in fewer bleeding episodes. No studies comparing the two drugs for DVT treatment exist; thus, this pharmacokinetic difference is difficult to relate to clinical practice. One study involving 440 patients that compared tinzaparin (4,500 antifactor IU Xa) and enoxaparin (40 mg) for prophylaxis of DVT after hip surgery identified four patients in the enoxaparin group and two patients in the tinzaparin group who experienced major bleeding.[7] Minor bleeding occurred in 21 patients in the enoxaparin group and in 13 patients in the tinzaparin group. This study showed a lower incidence of bleeding with tinzaparin; however, the difference was not statistically significant.

Because of its increased duration of action, tinzaparin can be given once a day vs. once-to-twice daily for enoxaparin (depending on its indication). This is an important pharmacokinetic difference in terms of cost and convenience.

Dosing

Recommended dose for treatment of DVT:[3,4]

Tinzaparin dose:

- 175 IU / kg SC QD

Enoxaparin dose:

- 1 mg / kg / dose Q12H
- 1.5 mg / kg / dose Q24H

Duration of therapy

Average duration of therapy for LMWH is 6-7 days. Warfarin therapy should be started between days 1-3 of LMWH therapy. Treatment with LMWH should continue until a therapeutic INR (between 2-3 for two consecutive days) can be achieved.

Renal impairment

Dose with caution in patients with severe renal impairment. In patients with moderate renal failure (CrCl 30-80 mL / min), antifactor-Xa clearance was similar to clearance in healthy patients. For patients with severe renal impairment (CrCl < 30 mL / min), clearance was 30% lower in enoxaparin patients and 24% lower in tinzaparin patients compared to controls. Although no recommendations have been made, dosage adjustments or alternate therapy should be considered in patients with severe renal impairment.[3,4,8]

Geriatric dosing

Because LMWHs are eliminated renally, elderly patients may have decreased elimination. Dose modification, however, is not necessary unless severe renal impairment exists.

Pediatric dosing

At this time, neither tinzaparin nor enoxaparin is approved by the FDA for use in pediatric patients.

As indicated in **Table 2, p. 3**, tinzaparin and enoxaparin have similar adverse effect profiles.[3,4] Slight differences in incidence of common side effects were not statistically significant in a trial comparing prophylaxis doses of tinzaparin and

enoxaparin.[7] In one tinzaparin study, major bleeding was reported as 0.5% with 175 antifactor Xa IU / kg daily for six days and 3% with unfractionated heparin. Incidence of minor bleeding was equal at 3% for both groups.[8] Studies with enoxaparin report a 2% rate of major bleeding.[4] Injection-site pain or irritation also is a common adverse effect, and case reports of skin necrosis have been reported with both tinzaparin and enoxaparin.[3,4]

Contraindications

Contraindications to outpatient therapy with LMWH include **(see Table 3, p. 4)**:[3,4]

- history of heparin-induced thrombocytopenia;
- presence of current thrombocytopenia;
- history of two or more episodes of DVT or PE;
- concurrent pulmonary embolism;
- significant comorbidity;
- contraindications to anticoagulants;
- inherited or acquired clotting or bleeding disorders;
- active bleeding;
- pregnant or lactating women;
- morbid obesity (actual body weight > 150 kg);
- renal insufficiency;
- inability to understand instructions or attend follow-up visits;
- history of protein C, protein S, or antithrombin III deficiency;
- potential for noncompliance; and
- lack of home support.

Precautions

Precautions that should be exercised when using tinzaparin and enoxaparin are detailed in **Table 4, p. 4**.[3,4]

Monitoring and management

Labs. Routine laboratory monitoring with aPT and aPTT is not necessary with LMWH products. Monitoring may become necessary if complications such as overdose or bleeding occur. Therapy with these agents can be monitored with measurements of antifactor-Xa activity per mL. Recommended target plasma range usually is 0.5-1.0 antifactor-Xa units, with peaks measured 3-4 hours after dose.[9] Complete blood counts (CBC) with platelets, hematocrit, and hemoglobin, and stool tests for occult blood should be assessed periodically. [3,4,8]

Overdose

Overdose with these products may result in bleeding complications. Patients with cases of minor bleeding or increased bruising should be monitored. Injected enoxaparin and tinzaparin can be neutralized with slow IV injection of protamine sulfate 1% solution (1 mg protamine

Table 2. Adverse effects

Adverse effects	Tinzaparin	Enoxaparin
Hematologic	Major bleeding associated with tinzaparin for DVT treatment with or without pulmonary embolism (PE) was 0.8% vs. 2.7% with unfractionated heparin.	Major bleeding episodes associated with DVT treatment with or without PE is approximately 2%.
Thrombocytopenia	• Has been reported to occur in 1% of patients on tinzaparin. • Severe thrombocytopenia (platelet count < 50,000/mm^3) was reported to occur in 0.13% of patients.	• Occurs with an incidence of 2%. • Moderate thrombocytopenia (platelet count 50,000-100,000/mm^3) occurs in 1.3% of the enoxaparin group and 0.6% of placebo group. • Severe thrombocytopenia (platelets < 50,000/mm^3) occurs in 0.1% of enoxaparin patients and in 0.0% of the placebo patients.
Elevated AST (aspartate aminotransferase), ALT (alanine aminotransferase)	Values 3x the upper normal limit have been reported for aspartate and/or alanine aminotransferase with an incidence of 8.8% and 13%, respectively.	Asymptomatic increases in aspartate and alanine aminotransferase levels greater than 3x the upper normal limit have been reported in 6.1% and 5.9% of patients, respectively.
Epidural hematoma	Patients receiving epidural or spinal anesthesia with LMWH are at risk for epidural hematomas that may result in paralysis. Risk increases with use of catheters in the spinal canal for administration of analgesics, traumatic or repeated epidural, spinal puncture, or use of drugs affecting hemostatis (e.g., NSAIDS, platelet inhibitors, and other anticoagulants). More than 30 occurrences have been reported to the FDA.	
Injection-site hematoma	Injection-site hematoma has been reported in 16% of patients. Incidence is dose-related.[14,19]	Injection-site hematoma is reported to occur in 9% of patients.

Table 3. Contraindications

Contraindications	Tinzaparin	Enoxaparin
Bleeding or clotting disorders	x	x
Hypersensitivity to product components (heparin, sulfite, benzyl alcohol, or pork products)	x	x
Active bleeding	x	x
Patients with neuroaxial anesthesia or spinal puncture	x	x
Thrombocytopenia	x	x

sulfate for each mg of enoxaparin or each 100 antifactor Xa IU of tinzaparin should be administered). An additional 0.5 mg of protamine sulfate per 1 mg of enoxaparin or 100 antifactor Xa IU of tinzaparin can be given if the aPTT (measured 1-2 hours after initial protamine infusion) continues to be increased. Additional doses of 1 mg protamine sulfate per 1 mg of enoxaparin have been given in case reports that suggest that additional doses be based on patient response rather than laboratory values. Administration of protamine sulfate does not result in 100% neutralization of antifactor Xa. Protamine sulfate achieves maximal neutralization at 60% with both LMWH products.[3,4]

Both tinzaparin and enoxaparin interact with the agents listed in **Table 5, p. 5**.[3,4,8] Use of these agents should be discontinued prior to LMWH therapy. If discontinuation is not possible, patients should be monitored closely for increased risk of bleeding. GI bleeding is a concern with these interactions.

Efficacy

A summary of important trials examining the efficacy of these drugs for DVT treatment is provided below.

Tinzaparin:

• The American-Canadian Thrombosis Study was a multicenter, randomized double-blind clinical trial that compared IV unfractionated heparin (UFH) and tinzaparin in patients with acute DVT.[10] Of 432 patients, 219 were in the UFH group and 213 were in the LMWH group. Patients at least 18 years of age with proximal DVT documented by venography were included. In addition to exclusion of patients with previously listed contraindications to LMWH therapy, patients who received warfarin, LMWH, or heparinoids in the seven days prior to the study, patients who received therapeutic doses of SC heparin within 12 hours prior to the study, patients who were receiving IV heparin, and patients who did not sign informed consent documents were excluded.

Subcutaneous tinzaparin (175 IU / kg) was found to be at least as efficacious as IV UFH for DVT treatment. UFH was dosed with an initial IV bolus dose of 5,000 USP units followed by continuous infusion of 40,320 or 29,760 units Q24H, depending on whether the patient had designated risk factors for bleeding. UFH dose was adjusted based on laboratory values of aPTT. Statistically significant differences were observed with recurrence of thromboembolism and major bleeding. Major bleeding with long-term warfarin therapy was higher with tinzaparin. The significance of this difference was not determined. Results of this study are illustrated in **Table 6, p. 5**.

Use of a standardized heparin protocol that achieves therapeutic levels in greater than 90% of patients during the first 24 hours was one strength of the study, because subtherapeutic doses of heparin can result in high rates of recurrent thromboembolism. Baseline characteristics of

Table 4. Precautions

Precautions	Tinzaparin	Enoxaparin
Caution in patients at risk of bleeding (including peptic ulcer disease, infective endocarditis, recent lumbar puncture, hypertensive or diabetic retinopathy, and severely uncontrolled hypertension)	x	x
Caution in elderly patients; consider dosing intervals, low body weight, concomitant medications, and predisposition to decreased renal function	x	x
Concomitant therapy with platelet inhibitors	x	x
Should not be mixed with other injections or infusions	x	x
Patients with minor bleeding or increased bruising should be monitored for signs and symptoms of severe bleeding	x	x
Not intended for IM or IV administration*	x	x*

* Enoxaparin currently is being investigated for IV administration.

Table 5. Drug interactions

Drug	Severity	Onset	Effect	Mechanism
Dipyridamole	Moderate	Rapid*	Increased risk of bleeding or hematoma with all drugs that alter hemostasis.*	Decreased platelet function*
NSAID	Major			
Oral anticoagulants	Moderate			Decreased coagulation*
Salicylates	Moderate			
Sulfinpyrazone	Moderate			

* Applies to all five drug classes.

patients in the groups were similar, and both fatal and nonfatal outcomes of the study were identified at various centers rather than at one center.

Two hundred patients from this same multicenter, double-blind, randomized study were evaluated for the treatment of PE and underlying DVT.[11] Patients were included based on presence of high-probability lung scan findings and regionally normal findings on chest radiographs. The treatment regimens were the same as those in the previous study group. Of the 200 patients with PE and underlying DVT, 97 patients were in the tinzaparin group, and 103 were in the UFH group. None of the tinzaparin patients had a recurrence of thromboembolism, while seven of the UFH patients experienced recurrence. Major bleeding occurred in one LMWH patient and two UFH patients; minor bleeding occurred in two LMWH patients and three UHF patients. Thrombocytopenia occurred with three LMWH patients and one UFH patient, while death occurred in nine UFH patients and six LMWH patients. Results were not specified as being statistically significant. However, it was concluded that tinzaparin is at least as efficacious as UFH therapy.

• The Tinzaparin or Standard Heparin: Evaluations in Pulmonary Embolism (THESEE) Study was a multicenter, randomized, unblinded clinical trial comparing once-daily tinzaparin and IV UFH.[12] For study inclusion, pulmonary embolism had to be documented objectively by pulmonary angiography, by ventilation-perfusion lung scanning indicating a high probability of pulmonary embolism, or by scanning with indeterminate results that were accompanied by DVT, which was confirmed by venography or compression ultrasonography.

The primary outcome measurements were death, symptomatic recurrent thromboembolism, or major bleeding measured eight days into the study. The endpoints were assessed again at day 90. Patients were excluded if they were thought to have a massive pulmonary embolism requiring thrombolytic therapy or pulmonary embolectomy, active bleeding, disorders contraindicating anticoagulation therapy, a therapeutic dose of anticoagulation therapy for more than 24 hours before entering the study, life expectancy of less than three months, severe hepatic or renal failure, likelihood of noncompliance, or pregnancy. Of 612 patients in the study, 308 patients were assigned to the UFH group and 304 patients received LMWH. Nine patients from each group reached at least one primary endpoint within the first eight days. By day 90, 22 and 18 patients from the UFH and tinzaparin groups, respectively, reached at least one of the clinical endpoints. None of these results showed a statistically significant difference; therefore, tinzaparin was proven to be at least as effective as UFH in DVT patients with PE. Selection criteria used in this study may have caused patients at higher risk for recurrences, bleeding, and death to be excluded. Results of this trial are presented in **Table 7, p. 6**.

Enoxaparin:

• A *New England Journal of Medicine* study conducted by Levine et al compared treatment of DVT with LMWH in outpatient settings with UFH administered in the hospital.[13] The study

Table 6. Results of the American-Canadian Thrombosis study

Results	UFH	Tinzaparin
Recurrent thromboembolism	15	6
PE in patients who had recurrence of thromboembolism	6 of 15	3 of 6
Major bleeding	11	1
Minor bleeding with long-term heparin	8	6
Major bleeding with long-term warfarin therapy	0	5
Minor hemorrhagic complications	4	5
Epistaxis	3	2
Thrombocytopenia	3	6
Deaths during three-month follow-up	21	10

Table 7. CAPRIE trial intention-to-treat analysis — primary and secondary outcome clusters

Outcome event cluster and treatment group		First outcome events			Event rate per year	Relative risk reduction	P value
		Nonfatal	Fatal	Total			
Ischemic stroke, MI, or vascular death (primary cluster)	Clopidogrel	631	308	939	5.32%	8.7%	0.043
	Aspirin	700	321	1,021	5.83%		
Ischemic stroke, MI, amputation, or vascular death	Clopidogrel	677	302	979	5.56%	7.6%	0.076
	Aspirin	737	314	1,051	6.01%		
Vascular death	Clopidogrel		350	350	1.90%	7.6%	0.29
	Aspirin		378	378	2.06%		
Any stroke, MI, or death from any cause	Clopidogrel	643	490	1,133	6.43%	7.0%	0.081
	Aspirin	720	487	1,207	6.90%		
Death from any cause	Clopidogrel		560	560	3.05%	2.2%	0.71
	Aspirin		571	571	3.11%		

included patients with acute proximal DVT confirmed by sonography or ultrasonography. Patients with contraindications to LMWH therapy or to outpatient therapy with LMWH and patients who had previous treatment with UFH for more than 48 hours or who did not provide informed consent were excluded. Of the 500 patients who met these criteria, 247 were assigned to the LMWH group and 253 were assigned to the UFH group. Results of this trial are presented in **Table 8, below**.

• A parallel-group, randomized, partially blinded, multicenter international trial conducted by Merli et al compared enoxaparin 1.0 mg/kg Q12H, enoxaparin 1.5 mg/kg Q24H, and UFH dosed according to institutional protocol in the treatment of DVT.[14] Patients had to be more than 18 years old to enter the study. Inclusion required symptomatic lower-extremity DVT. Exclusion criteria were related to contraindications to LMWH or warfarin therapy. Of the 900 patients who met the criteria, 290 were randomized to the UFH group, 298 to the once-daily enoxaparin (E1) group, and 312 to twice-daily enoxaparin (E2) group. Only 20 of the 136 patients who did not complete the study discontinued due to adverse effects (six with UFH, nine with E1, and five with E2). Twice-daily enoxaparin had more favorable results vs. both groups in every endpoint. Although differences in thromboembolism, major hemorrhage, and thrombocytopenia were not statistically significant,

Table 8. Summary of data on primary (safety) endpoint

Outcome event	Ticlopidine	Clopidogrel 75 mg QD	Clopidogrel 300/75 mg QD	Clopidogrel total
Composite (of all events)	31 (9.1%)	21 (6.3%)	10 (2.9%)	31 (4.6%)
Major peripheral or bleeding complications	4 (1.2%)	4 (1.2%)	5 (1.5%)	9 (1.3%)
Neutropenia	1 (0.3%)	0	0	0
Thrombocytopenia	0	2 (0.6%)	2 (0.6%)	4 (0.6%)
Early discontinuation due to noncardiac event	23 (6.2%)	17 (5.1%)	7 (2%)	24 (3.5%)
Skin disorder	9 (2.6%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Gastrointestinal disorder	9 (2.6%)	8 (2.4%)	1 (0.3%)	9 (1.3%)
Allergy	4 (1.2%)	0	0	0
Other	6 (1.8%)	6 (1.8%)	4 (1.2%)	10 (1.5%)

P values for the composite of primary endpoints:
P = 0.005 for ticlopidine vs. clopidogrel combined (both clopidogrel groups combined)
P = 0.001 for ticlopidine vs. 300/75 mg QD clopidogrel
P = 0.194 for ticlopidine vs. 75 mg QD clopidogrel
P = 0.043 for 300/75 mg QD clopidogrel vs. 75 mg clopidogrel

occurrences with E2 still were lower. Results of this study are presented in **Table 9, p. 7**.

• Another study compared enoxaparin (given in a fixed dose of 1 mg/kg Q12H) and UFH (given as an initial continuous infusion of 500 U/kg per 24H).[15] Patients were included in the study if they were older than 18 years with a proximal DVT proved by bilateral ascending venography. Exclusion criteria for the patients included associated severe pulmonary embolism requiring thrombolytic therapy, contraindications to anticoagulants, use of curative heparin therapy for more than 24 hours, recent surgery, pregnancy, previous implantation of vena cava filter, previously well-documented deficiency in coagulation inhibitors, and history of heparin-induced thrombocytopenia. Of the 134 patients who met the study criteria, 67 were randomized to the UFH group and 67 to the enoxaparin group. All patients were examined daily during the first 10 days of the study. Venograms from day 0 and day 10 were assessed and showed a significant difference favoring enoxaparin. In the UFH group, five venograms were found to have worsened, 34 were unchanged, and 18 improved, compared to one worsened, 24 unchanged, and 35 improved in the enoxaparin group. No patients in either group experienced major bleeding or recurrent DVT. Minor bleeding occurred in four enoxaparin patients and no UFH patients. According to this study, enoxaparin was more effective than UFH. Differences in outcomes measured were statistically significant.

• Both tinzaparin and enoxaparin have been shown to be more efficacious than UFH heparin in the treatment of DVT. Because no trials compare the two agents for this indication, direct comparison cannot be made. However, clinical experience demonstrates that both agents have been used efficaciously with similar safety profiles.

Cost

Treating patients with LMWH products allows patients to be discharged early or to be treated at home. This will decrease the number of hospital days and, thus, decrease cost.[16] **Tables 10 and 11, p. 7**, present drug cost information for enoxaparin and tinzaparin.

Enoxaparin:

1 mg/kg/dose Q12H

• For a 60 kg patient with a dose of 1 mg/kg Q12H, the patient should receive a 60 mg dose Q12H, which would result in a daily price of

$46.78 ($23.39 x 2). For an average six-day course of therapy, enoxaparin would cost $280.68 ($46.78 x 6).

• For a 75 kg patient, calculated in the same manner, a six-day course of therapy costs $374.16.

1.5 mg/kg/dose Q24H

• For a 60 kg patient with a dose of 1.5 mg / kg Q24H, the patient should receive a 90 mg dose, which would result in a daily price of $38.97. For an average six-day course of therapy, enoxaparin would cost $233.82 ($38.97 x 6).

• For a 75 kg patient, calculated in the same manner, a six-day course of therapy costs $303.90.

Tinzaparin:

175 IU/kg SC QD

• A 60 kg patient with a dose of 175 IU / kg Q24H requires 10,500 IU per dose. A six-day regimen requires 63,000 IU or two 2 mL vials. The cost per vial is $52.34. Thus, a six-day course of therapy with tinzaparin would be $104.68 ($52.34 x 2).

• A 75 kg patient requires 78,750 IU, which also is two mL vials. A six-day course of therapy for this patient also would be $104.68.

Cost comparison

• The cost difference between enoxaparin and tinzaparin for an average six-day regimen for a 60 kg patient is $176 ($280.68-$104.68) for outpatient therapy. The cost difference for a 75 kg patient is $269.48 ($374.16-$104.68).

• Use of tinzaparin for DVT treatment can significantly reduce the cost of therapy. The direct drug cost saving of tinzaparin over enoxaparin is less with the once-daily (inpatient) dose of enoxaparin compared to the twice-daily dose. However, cost of hospitalization also must be considered with use of the inpatient dose.

Table 10. Drug cost: Enoxaparin

Available doses	Cost per dose
30 mg/0.3 mL	$11.68
40 mg/0.4 mL	$15.57
60 mg/0.6 mL	$23.39
80 mg/0.8 mL	$31.18
100 mg/mL	$38.97

Table 11. Drug cost: Tinzaparin

Available dosage form	Cost per vial
2 mL vial (40,000 IU/2 mL)	$52.34

Table 9. Results of the Merli et al study

Results	E1	E2	UFH
Recurrent thromboembolism	13 (4.4%)	9 (2.9%)	12 (4.1%)
Venous thromboembolic disease	11 (4.5%)	8 (3.1%)	10 (4.3%)
Death	11 (3.7%)	7 (2.2%)	9 (3.1%)
Thrombocytopenia	1	0	0
Major hemorrhage	5 (1.7%)	4 (1.3%)	6 (2.1%)

• Because tinzaparin is available only in one vial size (40,000 IU / 2 mL vial), the potential for drug wastage with weight-based dosing exists. However, individual tinzaparin doses can be drawn up in plastic syringes, and are stable for 10-15 days under refrigeration or at room temperature.[17] By preparing specific doses from the 2 mL vial, drug wastage can be reduced, and cost savings can be realized to a greater extent.

Conclusion

The major differences in tinzaparin and enoxaparin are those of a pharmacokinetic nature. The difference in the antifactor-Xa / IIa ratio theoretically could account for differences in anticoagulation efficacy, as well as differences in the incidence of bleeding. Pharmacokinetic differences do exist and are reflected by differences in the respective dosage regimens of each LMWH. Both tinzaparin and enoxaparin have proven to be efficacious in clinical trials for DVT treatment compared to UFH. Comparable rates of adverse events and efficacy have been noted.

Thus, the pharmacokinetic differences have not translated to improved clinical response. However, enoxaparin demonstrates more experience in clinical trials than tinzaparin.

LMWH products proven efficacious can be given at recommended product-specific doses. However, LMWHs should be considered separate anticoagulation products and should not be interchanged on a dose-per-dose basis. Although no head-to-head trials have been conducted for these products for DVT treatment, both agents have been proved safe and effective.

Thus, cost and experience become important factors in the decision to add tinzaparin to the formulary. The potential for significant cost reductions with the use of tinzaparin supports the consideration of its addition to the formulary / DVT outpatient protocol.

References

1. Diaz-Linares M, Rodvold K. Coagulation disorders. In: DiPiro JT, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 4th ed. New York: Elsevier Science Publishing Co.; 1989:1549-1572.

2. Tapson V. Deep venous thrombosis: Outpatient therapy with low-molecular-weight heparin. *Manag Care* 1999; 8(Suppl):S2-S6.

3. DuPont Pharmaceutical Co. Tinzaparin product compendium. Wilmington, DE: 2000.

4. Rhone-Poulenc Rorer Pharmaceuticals. Enoxaparin package insert. Collegeville, PA: 1999.

5. Cornelli U, Fareed J. Human pharmacokinetics of low-molecular-weight heparins. *Sem Thromb Hemost* 1999; 25(Suppl 3):57-60.

6. Helena B, et al. Preclinical differentiation of low-molecular-weight heparins. *Sem Thromb Hemost* 1999; 25(Suppl 3):63-72.

7. Planes A, et al. Prevention of deep vein thrombosis after hip replacement — Comparison between two low-molecular heparins, tinzaparin and enoxaparin. *Thromb Haemost* 1999; 81:22-25.

8. Enoxaparin [monograph in electronic version]. *Micromedex Healthcare Series*. Englewood, CO: Micromedex; 2001.

9. Low-molecular-weight heparin for venous thromboembolism. *Drug Ther Bull* 1998; 36:25-29.

10. Hull R, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 1992; 326:975-982.

11. Hull R, et al. Low-molecular-weight heparin vs. heparin in the treatment of patients with pulmonary embolism. *Arch Intern Med* 2000; 160:229-236.

12. Simonneau G, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med* 1997; 337:663-669.

13. Levine M, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996; 334:677-681.

14. Merli G, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* 2001; 134:191-202.

15. Simonneau G, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. *Arch Intern Med* 1993; 153:1541-1546.

16. Personal communication. Cindy Hall, buyer, Pharmacy Department, Huntsville Hospital System; May 2001.

17. Innohep-DuPont Pharmaceuticals. Available at http://www.innohep.com. Accessed Nov. 2, 2001.

18. Liezorovicz A, et al. Prevention of perioperative deep vein thrombosis in general surgery: A multicentre double blind trial comparing two doses of Logiparin and standard heparin. *Br J Surg* 1991; 78:412-416.

19. Siegbahn A, et al. Subcutaneous treatment of deep venous thrombosis with low-molecular-weight heparin: A dose finding study with LMWH-Novo. *Thromb Res* 1989; 55:767-778. ■

IN THE PIPELINE

• Alexion Pharmaceuticals is preparing to initiate a Phase III clinical trial of pexelizumab in approximately 3,000 patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass. The trial will assess the safety and efficacy of pexelizumab in reducing the combined incidence of **death** and **myocardial infarction** in this patient population.

• Neurocrine Biosciences has initiated the first Phase III clinical trial of NBI-34060 in approximately 500 patients with **chronic (primary) insomnia**. The Phase III clinical trial is a randomized, double-blind, parallel-group, multicenter study that will evaluate the safety of two doses of NBI-34060 Immediate Release for the long-term treatment of chronic insomnia in adults. The trial will be conducted at approximately 40 medical sites in the United States and Europe.

• Isis Pharmaceuticals has initiated clinical testing of ISIS 104838, an antisense inhibitor of tumor necrosis factor-alpha (TNF-alpha), in **rheumatoid arthritis** (RA). This Phase II clinical trial will evaluate the ability of ISIS 104838 to reduce the level of TNF-alpha in synovial tissue, the autoimmune target tissue involved in RA, and in blood. The study also will evaluate the biological effect of TNF-alpha inhibition by ISIS 104838 in RA.

• Protein Design Labs has initiated a Phase II clinical study to evaluate its humanized antibody daclizumab (Zenapax) in patients who suffer from **chronic, persistent asthma** and whose disease is not well controlled with high doses of inhaled corticosteroid therapy. The randomized, double-blind, placebo-controlled clinical trial will be conducted at approximately 22 centers in the United States, with a target enrollment of 120 patients. ■