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DRUG UTILIZATION REVIEW™

Pharmaceutical Care Across the Continuum

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Pharmacists will participate more in patient care in years to come

Provider status legislation still high on the lists of pharmacy groups

With a new year unfolding, *Drug Utilization Review* (*DUR*) takes this opportunity to look ahead at pharmacy practice, regulation, and the continued battle for pharmacists to receive provider status. To help, *DUR* asked representatives from the American Society of Health-System Pharmacists (ASHP) in Bethesda, MD, and the American Pharmaceutical Association (APhA) in Washington, DC, for their thoughts. Here is what they said.

Pharmacy practice

Pharmacists will continue to have a more active role in patient care in a variety of settings, says **David Witmer**, PharmD, director of ASHP's professional practice and scientific affairs division. "As more pharmacists complete residency training and as more pharmacists graduate with PharmD degrees, you'll see increased interest and increased activity in those areas. Is that going to mean there will be more pressures to look at the system of health care and how we use pharmacists, how we use technicians and technology? Sure."

Witmer expects that a number of pharmacists who have graduated with bachelor of science degrees will seek some additional degree. That may or may not be the PharmD degree, however. "You will see pharmacists continuing to pursue master's degrees and PhDs and other degrees to further their career. What direction they will go in their post-graduate education would really depend on their career interest."

More pharmacists with PharmD degrees will pursue advanced degrees, as well, he continues. "As long as we have pharmacists, we are going to have pharmacists who want to better themselves and further their education. I don't think that is going to change. What will change is the number of baccalaureate graduates in the work force over time."

Witmer also expects an increase in the emphasis on appropriate education and training of pharmacy technicians and increased credentialing of those technicians through the technician certification exam. That will lead to more well-defined roles for technicians in a variety of settings and will enable pharmacists to apply their time more effectively in other

patient care activities, he says.

Other trends may stay in the forefront in the near future, Witmer says. These include:

• Popular prescription drugs shifting to over-the-counter (OTC) status.

The debate about switching prescription drug products to OTC status will continue, Witmer predicts. "That will have some impact in terms of patient care and in terms of pharmacists having to address how those drugs will be used, what their formulary status will be, and how patients will get their OTC medications for a number of different disease states."

"Claritin moving OTC is going to be a significant shift, and Prilosec is on track to move over as well," says **Susan Winckler**, RPh, JD, vice president of policy and communications and staff counsel for APhA. However, she adds, the reality is that all health care is what could be called "self-care," because it ultimately depends on what the patient chooses to do. "Certainly the increasing availability of over-the-counter medications presents another opportunity for pharmacists to make the best use of those over-the-counter medications."

• New advice coming out on handling cytotoxic drugs.

"There is some emerging research about transferring devices and protections from various types of biological safety cabinets," Witmer says. "That will begin to have impact in the next year on people thinking about how they set up their program and how they prepare those drugs in various work settings."

Regulation

The biggest challenge in the first quarter of 2003 will be making sure everyone is ready for compliance with the final federal privacy regulation in mid-April, Winckler says. The privacy regulation is mandated under the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

"That requires folks to be taking a look at how they deal with their information, developing privacy practices, developing information that communicates those privacy practices to their patients, and then tracking all that information, as well," she says.

The portion of the rule that addresses distributing notice of privacy practices and then documenting that patients have received it is difficult because it's not standard practice today, she says. However, it's still better than what could have been. "[That section] is far superior to the prior written consent requirement. It's superior for patients because they won't have this disruption to their care, and obviously superior for the care providers because they can actually focus on caring for their patients rather than chasing a paper requirement that may not have yielded much benefit."

Winckler expects the HIPAA security and electronic signature standards to be released soon, but providers should have a greater implementation period for these standards than for the privacy rules, which were released in August and had an implementation date of April.

Regulation may be forthcoming on the issue of pharmacist compounding, as well, Witmer says. "There will be some potential challenges or changes to either state board of regulations or FDA [U.S. Food and Drug Administration] policies that could affect how pharmacists practice in the coming year."

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Prescription drug costs expected to rise 20%

Americans go outside U.S. to buy cheaper drugs

The cost of prescription drug coverage is expected to continue to increase at a rate of nearly 20% in 2003, according to a report released in late November.

The "2003 Segal Health Plan Cost Trend Survey" reports projections for 2003 obtained from a survey of major insurance carriers, managed care organizations, pharmacy benefit managers, and third-party administrators. For people younger than age 65, retail prescription drug costs are projected to increase by 19.5%, and mail-order costs are projected to increase by 18.9%. For retirees older than 65, retail prescription drug costs are expected to increase by 19%, and mail order costs by 19.3%. If the actual 2003 costs match the projection, the cumulative effect of prescription drug trend increases since 1999 will have been an increase of almost 100% over five years.

Key factors driving the overall projected increases were price inflation and increased utilization in several major drug categories, such as antidepressants, antihistamines, antilipids, and gastrointestinal medication. Other factors contributing to the increase in prescription drug trends include:

- increased patient demand and education as a result of direct-to-consumer advertising and other pharmaceutical marketing or promotional efforts;
- increased prescribing in the antilipid and anti-ulcer drug categories;
- efforts by drug manufacturers to increase market share and extend single-source brand use;
- the introduction of improvements over existing therapies;
- the introduction of new and expensive drug therapies and greater reliance on drug therapy by the physician community;
- an aging work force;
- increased obesity among all age groups;
- improved techniques and technology to detect and diagnose diseases; and
- the erosion of enrollee cost-sharing in plans with fixed copayments.

For more information about the report, see www.segalco.com/publications/surveysandstudies/2002trendsurvey.pdf.

Drugs outside U.S. attractive

A recent poll found that if drug costs continue to rise, many Americans (40%) would go outside the country — either in person, by mail, or through the Internet — to buy cheaper drugs. This percentage in the *Wall Street Journal Online*/Harris Interactive Health-Care Poll jumps to 51% among those who spend more than $2,000 per year on prescription drugs.

Five percent of Americans are making drug purchases outside of the country already, and 21% of those who have spent in excess of $2,000 per year on prescription drugs have shopped abroad to find better drug prices. This is a "catastrophe waiting to happen" for the drug industry because its profits depend heavily on the U.S. market, says Humphrey Taylor, chairman of The Harris Poll, Harris Interactive. "This trend is likely to grow as out-of-pocket costs rise because of increased co-pays, coinsurance, deductibles, and the growing use of tiered formularies."

Not many people (11%) are worried about the safety of drugs bought in Canada, the poll shows. "It would take a major scandal concerning the safety of drugs sold outside the U.S. to slow this trend, and many experts believe it would be extremely difficult to prevent people from buying drugs on-line from other countries," Taylor says. ■

In June, the Foodand Drug Administration (FDA) issued a compliance policy guide for FDA staff and industry regarding pharmacy compounding. (To see the report, go to www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-200.html.)

Efforts to address compounding on the state level can be of benefit if they are done well, Winckler says. The challenge is that the FDA regulates manufacturing, not compounding. "We have to work out some middle ground there. We certainly don't want to protect the folks who are manufacturing under the guise of compounding. We hope the FDA identifies them without sweeping the whole profession and the activity we call 'compounding' under

that umbrella of activity."

Another issue Winckler expects to undergo intense debate in the near future is the effort to speed the availability of generic drugs. A Senate bill passed in July 2001 is dead because the House failed to act on it. An administration plan is moving forward, but the question remains as to whether the plan is strong enough.

"That will likely be debated between the generic manufacturers and the brand-name manufacturers," Winckler says. "From the pharmacists' perspectives, [the question is] how do we make sure there is protection for the brand-name companies so we will continue to have innovative medications, but still get rid of some of the so-called loopholes that have really challenged the system? Obviously, pharmacists want their patients to have access to good-quality generics."

The battle will continue over a Medicare prescription drug discount plan, as well. A hearing was scheduled for late January on whether the Bush administration has the regulatory authority to conduct this program.

Provider status

Some of the biggest challenges are going to come not in the form of government regulation, but in government's role as a payer and the regulations that result, Winckler says. In Medicare, there continues to be an effort to add a Medicare benefit that will pay pharmacists for their services.

Securing provider status for pharmacists under the Social Security Act has been a major effort for ASHP, Witmer says. "We think that is important because, particularly in ambulatory care settings, pharmacists just aren't on the same par as other types of providers who are providing the same kind of services but are able to bill for them."

When pharmacists are finally recognized, there will be significant impact on how pharmacists bill for their services and even on what kinds of services they can provide in what kinds of settings, Witmer adds. "It's not that they aren't trained to do that now, but they will be in a better economic position to justify their role in their services and obtain reimbursement for their services." ■

Loratadine (Claritin) gets OTC status

Critics fear increase in sedating antihistamine use

As expected, the U.S. Food and Drug Administration (FDA) has given loratadine (Claritin) over-the-counter (OTC) status. Loratadine, the only nonsedating antihistamine available OTC, is approved for seasonal allergic rhinitis.

The FDA's decision last November enables "many people to get less-sedating, effective relief for their allergy symptoms more quickly and at a lower cost," according to **Mark B. McClellan**, MD, PhD, commissioner of Food and Drugs. The price of OTC loratadine was expected to drop by as much as 76%, from as much as $3.80 a pill in its prescription form to about 92 cents and $1.17 a tablet OTC.

For a drug to be approved for OTC marketing, the FDA must determine that:

- the drug in question treats a condition that consumers can diagnose and manage themselves;
- the drug is sufficiently safe for use by consumers without direct prescriber supervision;
- the drug's label explains potential adverse effects and conditions of use with clear and understandable directions.

The FDA, according to loratadine manufacturer Schering-Plough, approved all five formulations of the Claritin brand at their original prescription strengths. These formulations include: Claritin Tablets, a once-daily formulation; Claritin RediTabs Tablets, a once-daily formulation in an orally disintegrating tablet; Claritin-D 24-Hour Extended Release Tablets, a once-daily formulation with a decongestant; Claritin-D 12-Hour Extended Release Tablets, a twice-daily formulation with a decongestant; and Claritin Syrup, a liquid formulation for use in children 2 years of age and older. The products were to be available by mid-December. Once loratadine OTC is available, all versions of the drug, either branded or generic, will only be sold over-the-counter. Schering-Plough's patent for loratadine expired Dec. 19.

The company says it intends to support loratadine as an OTC product with an educational program focusing on allergies, allergy management, and potentially associated conditions, such as asthma. The program also will provide allergy sufferers with recommendations about when to remain in close communication with their treating physician.

In addition, Schering-Plough says it has received an "approvable" letter from the FDA for the use of loratadine as an OTC treatment

for hives. The company must provide more information about the labeling for this indication before final approval can be given.

The implications of self-medication

Not everyone was pleased that the FDA gave loratadine OTC status. The National Consumers League in Washington, DC, expressed concern that once loratadine goes OTC, it is only matter of time before the FDA grants other non-sedating antihistamines (NSAs) the same status. (WellPoint Health Networks in Thousand Oaks, CA, had petitioned the FDA for OTC status for three leading prescription non-sedating antihistamines.)

"The consequence of this forced OTC shift, along with the other NSAs that WellPoint has petitioned on, would be to eliminate insurance coverage for the entire class of NSAs, reduce allergy patient contact with their physicians, and most likely encourage considerable numbers of allergy patients to choose cheaper, sedating antihistamines," maintains NCL president **Linda Golodner**, in a letter delivered to the FDA.

The American College of Allergy, Asthma, and Immunology (ACAAI) in Arlington, IL, says patients may be more likely to self-diagnose and self-medicate with the OTC loratadine. As a consequence, they may seek medical advice and care much later when their disease is more advanced and when they are at greater risk of comorbidities such as asthma and sinusitis. "Diagnosis and treatment of allergic diseases often require expert professional evaluation and advice," the ACAAI says in a statement.

Like the National Consumers League, the ACAAI also is concerned that increasing out-of-pocket costs for NSAs by either forcing patients to buy them OTC or to pay higher co-pays for the remaining prescription NSAs will result in some patients turning to less expensive antihistamines, which cause drowsiness.

For more information about popular prescription drugs going OTC, see the November 2002 issue of *Drug Utilization Review*. ■

Vaccine shows promise in preventing cervical cancer

Follow-up shows 100% effectiveness rate

An investigational vaccine has reduced the incidence of both human papillomavirus type 16 (HPV-16) infection and HPV-16-related cervical intraepithelial neoplasia (pre-cancer of the cervix), according to research published in the Nov. 21, 2002, issue of the *New England Journal of Medicine*.

In the double-blind study, none of the women who were vaccinated and had not been previously infected with HPV-16 became infected, whereas 3.8% of those who were not vaccinated developed HPV infection each year. "Immunizing HPV-16-negative women [with the vaccine] may reduce their risk of cervical cancer," the researchers concluded.

HPV-16 is the most common type of HPV linked to cancer; it is present in 50% of cervical cancers and high-grade cervical intraepithelial neoplasias and in 25% of low-grade cervical intraepithelial neoplasias. The monovalent vaccine, intended to prevent infection by HPV-16, contains virus-like particles that are devoid of DNA and are not infectious. However, they still generate a potent immune response.

To study the vaccine, researchers included 1,533 women ages 16-23 in the primary analysis. The women were not pregnant, reported no prior abnormal Pap smears, and reported that they had had no more than five male sex partners during their lifetime. They were randomly given either three doses of placebo or the HPV-16 vaccine, at day 0, month 2, and month 6.

The primary endpoint was persistent HPV-16 infection, defined as the detection of HPV-16 DNA in samples with use of polymerase chain reaction. At least 31 cases of persistent HPV-16 infection were required for the study to show a statistically significant reduction in the primary endpoint. This occurred at about two years into the study. The women will continue to be followed for a total of four years.

The women were followed for a median of 17.4 months after completing the vaccination regimen. All 41 cases of HPV-16 infection, including nine cases of HPV-16-related cervical intraepithelial neoplasia, occurred in the placebo group.

An accompanying editorial in the *New England Journal of Medicine* praised the research. "Five HPVs — types 16, 18, 31, 33, and 45 — are responsible for most cervical cancers. If women were vaccinated against these types of HPV before they became sexually active, there should be a reduction of at least 85% in the risk of cancer

and a decline of 44% to 70% in the frequency of abnormal Papanicolaou smears attributable to HPV. Because the more pernicious cancers appear most often with HPV-16 and HPV-18, the level of protection from death due to cervical cancer could exceed 95%," says **Christopher P. Crum**, MD, director of women's and perinatal pathology division at Brigham and Women's Hospital in Boston.

An advance such as an effective vaccine against HPV could have profound results on the current standard of care, he continues. "If the promise implicit in the study by Koutsky et al is realized, we could, in our lifetime, see the gradual but progressive dismantling of the barriers to preventing cervical cancer. The captives of our current system — both patients and their caregivers — may be set free."

Merck Research Laboratories, which manufactures the vaccine, funded the research and also has financially supported some of the researchers. ■

APhA awarded contract to establish Support Center

The American Pharmaceutical Association in Washington, DC, has been awarded a contract by the U.S. Department of Health and Human Services to establish the Pharmacy Services Support Center (PSSC) under the direction of the Office of Pharmacy Affairs within the Health Resources and Services Administration (HRSA).

The purpose of the PSSC is to streamline national support and expertise in the delivery of pharmacy advice and technical assistance for community health centers, HIV/AIDS drug assistance programs, hemophilia treatment centers, and other eligible HRSA grantees.

Some components of the project include: assisting the agency in determining its role in the pharmacy benefit under Medicare, assessing state pharmaceutical assistance programs, providing networking opportunities with key pharmacy groups, and developing educational materials to measure improved quality outcomes and reduce medication errors. Diane Goyette, RPh, JD, has been named the senior director of the center. ▼

Wyeth stops producing two vaccines

Wyeth announced in November that it was ceasing production of two of its vaccine products: FluShield, an injectable influenza virus vaccine, and Pnu-Imune, an injectable polysaccharide pneumococcal vaccine for adults.

Wyeth says adequate supplies of injectable flu vaccine are now available in the United States as a result of recent capacity increases provided by other manufacturers. Aventis Pasteur's Swiftwater, PA, facility, which currently produces about half the influenza vaccine used in the United States, has voiced its commitment to meeting U.S. demand. PowderJect Pharmaceuticals in England also supplies the flu vaccine.

The company says it has chosen to pursue new flu immunization technologies, such as its intranasal influenza vaccine. Ending production of the vaccines will allow it to reallocate resources to resolving the nine-month shortage of Prevnar, its pneumonia vaccine for young children, and winning regulatory approval for the nasal flu vaccine, a Wyeth spokesman told the Associated Press. ▼

Pharmacist participation in rounds cuts errors

A recent study found that including a clinical pharmacist on daily patient rounds cut medication errors by about 50%. The article, published in the Nov. 1, 2002, issue of the *American Journal of Health-System Pharmacy*, also found that pharmacists' interventions decreased the duration of errors.

In the study, a clinical pharmacist participated in daily rounds on one of the 19 medical services in an academic medical center for one month. The pharmacist investigated allergy information, monitored trends in laboratory test values, and

reviewed medication orders for appropriate medication selection and dose. The pharmacist also reviewed drug indications; patient age, weight, and organ function; and the medication administration record.

At the same time, a team of three reviewers examined all patients' medical charts for errors, including variances in medication selection, dosing, and monitoring from recommendations published in the institution's clinical staff manual. Reviewers classified the errors as prescribing, administration, pharmacy, or discharge errors. Overall, 46 errors occurred in the intervention group, while 94 errors occurred in the control group.

The number of patients without a medication error during their hospital stays also increased to 40%. In addition, the interventions affected how long an error continued after it occurred. An error persisted less than one day and with less than one dose of medication in the study group, compared with 2.4 days and two doses of medication for patients in the control group.

To read more about the study, go to www.ashp.com. ▼

Warnings strengthened on three medications

The Food and Drug Administration and Novartis have strengthened the labeling for Cafergot, a combination of ergotamine and caffeine. Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of Cafergot with potent CYP3A4 inhibitors, including protease inhibitors and macrolide antibiotics.

The revised label includes a new boxed warning and updates to the contraindications, warnings, precautions, and clinical pharmacology sections of the prescribing information. To read the full MedWatch 2002 safety summary, go to www.fda.gov/medwatch/SAFETY/2002/safety02.htm#caferg.

In addition, the FDA and Pharmacia/Pfizer have strengthened the contraindications, warnings, and adverse reactions sections of the prescribing information for valdecoxib (Bextra). In post-marketing experience, rare reports of hypersensitivity reactions (such as anaphylactic reactions and angioedema) and skin reactions, including cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and erythema multiforme, have been received. These cases, some of which were serious/life-threatening, have occurred in patients with and without a history of allergic-type reactions to sulfonamides. To read the MedWatch 2002 Bextra safety alert, go to: www.fda.gov/medwatch/SAFETY/2002/safety02.htm#bextra.

Finally, the FDA and MedImmune have revised the warnings, overdosage, and post-marketing experience sections of the palivizumab (Synagis) label to provide clarification on the risk of anaphylaxis based on worldwide post-marketing experience. The labeling was revised to reflect that adverse events after a sixth or subsequent dose of palivizumab are similar in character and frequency to those reported after the initial five doses. To read the full safety summary, see: www.fda.gov. ▼

Certain medication errors more likely to be harmful

Certain types of medication errors are more likely to cause harm or death to patients, according to a data report released in December by the United States Pharmacopeia's (USP) Center for the Advancement of Patient Safety (CAPS) in Rockville, MD.

"Summary of Information Submitted to MedmarxSM in the Year 2001: A Human Factors Approach to Medication Errors" is the third annual

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analysis of medication error reports by Medmarx, the national reporting database operated by USP. Medmarx is an Internet-accessible, anonymous medication error reporting program and quality improvement tool used to track medication errors.

Though the Medmarx data report relatively few errors (2,539/105,603 or 2.4%) resulted in harm in 2001, the report found that more cases of patient harm ensued when hospital staff applied incorrect administration techniques with medication and administered incorrect dosages of drugs. In addition, medication errors frequently involved high-alert medications. The report indicates that the top five products involved in harmful errors are the high-alert medications insulin, morphine, heparin, warfarin, and potassium chloride.

"Our data indicate that the wrong administration technique, such as the improper dilution of IV products, was almost four times more likely to cause harm in hospital patients," says **Diane Cousins**, RPh, vice president of CAPS at USP.

Of the 2,539 harmful errors, 353 required initial or prolonged hospitalization, 70 required intervention to sustain life, and 14 resulted in death. Patients involved in these harmful errors received intensive patient care, which triggered longer hospital stays, extensive testing, additional patient monitoring, and increased drug therapy.

For more information, visit the USP web site at www.usp.org. ■

New FDA Approvals

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

• *Nitazoxanide (Alinia) by Romark Laboratories.* The FDA has approved nitazoxanide (Alinia) Oral Suspension for treatment of children with **diarrhea** caused by *Cryptosporidium parvum* and *Giardia lamblia*. Nitazoxanide is the first and only drug approved by FDA for treatment of *Cryptosporidium*, and the first new drug approved for *Giardia* in more than 40 years. The product will be available in pharmacies in February 2003.

Alinia for Oral Suspension (100 mg/5 mL) will be available in a pleasant-tasting, easy-to-use liquid suspension form. A short, three-day treatment has been approved by the FDA for treating diarrhea caused by *Cryptosporidium* and *Giardia* in children ages 12 months to 11 years.

In placebo-controlled clinical studies, the side effects experienced by children receiving Alinia were not significantly different from those receiving a placebo. Safety and effectiveness of Alinia have not been studied in children younger than 12 months of age or older than 11 years of age, or in adults. In addition, safety and effectiveness have not been established in patients with immune deficiencies such as patients with human immunodeficiency virus.

• *New indication for rabeprazole sodium (Aciphex) by Eisai and Janssen Pharmaceutica*. Rabeprazole sodium (Aciphex), a proton pump inhibitor (PPI) widely prescribed for gastroesophageal reflux disease, is now approved by the FDA as part of the first seven-day treatment for ***Helicobacter pylori* infection**. Taken in combination with certain antibiotics, rabeprazole sodium treats *H. pylori* in up to half the time of current 10- to 14-day treatments. ■

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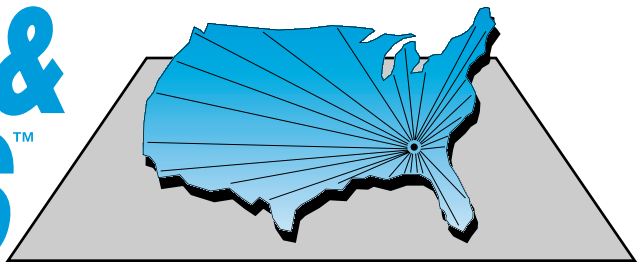

Fondaparinux Sodium (Arixtra) Drug Evaluation

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Background

Fondaparinux sodium (Arixtra) is the first of a new class of synthetic antithrombotic agents, known as the selective Factor-Xa inhibitors.

Mechanism of action

Fondaparinux binds to antithrombin III (ATIII) with a selectivity of 94%. This produces a conformational change of ATIII, which increases the affinity between ATIII and Factor Xa. After the ATIII-fondaparinux complex has bound Factor Xa, the fondaparinux component is released unchanged and is free to bind more ATIII.

Enoxaparin (Lovenox) and dalteparin (Fragmin) affect both Factor Xa and Factor IIa and are classified as low molecular weight heparins (LMWHs). Their mechanism is to bind preferentially to ATIII, produce a conformational change, and increase the affinity to Factor Xa, very similar to fondaparinux. The difference between the LMWHs and fondaparinux lies within the affinity to Factor Xa. Fondaparinux was designed to have an advantage of higher specificity to ATIII over LMWHs and thus decrease clot formation compared with LMWHs.

Indications

Table 1, below, lists FDA-approved indications for fondaparinux, enoxaparin, and dalteparin.[1-6]

Pharmacokinetics

A pharmacokinetic comparison of fondaparinux, enoxaparin, and dalteparin can be found

Table 1. FDA-approved indications

Indications	Fondaparinux	Enoxaparin	Dalteparin
Prophylaxis			
Hip fracture surgery	✗		
Hip replacement surgery	✗	✗	✗
Knee replacement surgery	✗	✗	
Abdominal surgery		✗	✗
Medically ill		✗	
Treatment			
Venous thromboembolism (VTE)		✗	
Unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI)		✗	✗

Table 2. Pharmacokinetic comparison of fondaparinux and LMWHs

	Fondaparinux	Enoxaparin	Dalteparin
Bioavailability	100%	92%	87%
C_{max}	3 hr	3-5 hrs	3-4 hrs
$T_{½}$	17-21 hrs	4-5 hrs	3-5 hrs
Clearance	Renal	Renal	Renal

in **Table 2, above**.[4-8]

Since fondaparinux has a half-life of 17-21 hours, its dosing is every 24 hours. This can be a disadvantage, however, if the patient is over-anticoagulated. Currently, there is no known antidote to reverse the effects of fondaparinux and therefore no pharmacological mechanism for its reversal.

Special populations

• **Elderly:** Due to natural decreases in renal function in the elderly population, the elimination of enoxaparin and fondaparinux may be prolonged. Dalteparin has not shown a difference in elimination profile based on age.

• **Body weight:** Fondaparinux is contraindicated in patients weighing less than 50 kg.[3] In this population, the total clearance of fondaparinux is decreased approximately 30%, increasing the patient's risk of bleeding.[2,3]

Body weight is mentioned as a precaution with enoxaparin (in patients weighing less than 45 kg) and with dalteparin (in patients weighing less than 50 kg); a dosage adjustment for weight is recommended for both agents.[4,5]

• **Renal/hepatic impairment:**

— Fondaparinux: Fondaparinux is contraindicated in patients with severe renal dysfunction (CrCl < 30 mL/min). Patients with any renal insufficiency (CrCl < 80 mL/min) may have decreased clearance of fondaparinux, so these patients should be monitored closely for any adverse reaction.

Hepatic impairment dosage adjustments have not been studied.[2,3]

— Enoxaparin: Dosage adjustment is advised for severe renal impairment (CrCl < 30 mL/min); specific recommendations are not given.

— Dalteparin: Precautions should be taken in patients with liver or renal impairment.

Specific recommendations are not given.

• **Pregnancy:** Fondaparinux, enoxaparin, and dalteparin are Pregnancy Category B agents.

Drug interactions

Fondaparinux and the LMWHs do not significantly affect the CYP450 isoenzymes or have a high degree of protein binding (less than 10%), which most often is responsible for drug interactions. However, there is a possible increase in the risk of bleeding when using LMWHs concurrently with other medications that affect hemostasis, such as oral anticoagulants, sulfinpyrazone, salicylates, nonsteroidsal anti-inflammatory drugs (NSAIDS, particularly ketorolac), and dipyridamole. Fondaparinux product information does not mention these interactions, although they potentially do exist.[2,3]

Adverse drug reactions

The most common adverse event with fondaparinux is bleeding. Listed below are adverse

Table 3. Contraindications

	Fondaparinux	Enoxaparin	Dalteparin
Hypersensitivity			
Drug	✗	✗	✗
Pork		✗	✗
Heparin		✗	✗
Active major bleeding	✗	✗	✗
Thrombocytopenia	✗	✗	✗
Severe renal impairment (less than 30 ml/min)	✗		
Body weight less than 50 kg	✗		
Bacterial endocarditis	✗		
Cerebral aneurysm			✗
Severe uncontrolled hypertension			✗

Table 4. FDA-approved dosages/indications

Indications	Dosage		
	Fondaparinux	Enoxaparin	Dalteparin
Prohylaxis			
Hip fracture surgery	2.5 mg SQ qd		
Hip replacement surgery	2.5 mg SQ qd	30 mg SQ bid 40 mg SQ qd	2500 IU before surgery then 5000IU SQ qd
Knee replacement surgery	2.5 mg SQ qd	30 mg SQ bid	
Abdominal surgery		40 mg SQ qd	2500IU SQ qd unless high risk
Medically ill		40 mg SQ qd	
Treatment			
VTE		Outpatient 1 mg/kg SQ q12h Inpatient 1.5 mg/kg SQ qd	
UA/NSTEMI		1 mg/kg SQ q12+ ASA 100-325 mg qd	120 IU/kg SQ BID+ ASA 75-165 mg/d

effects derived from all clinical trials according to the clinical compendium distributed by the manufacturer of fondaparinux.[2]

	Fondaparinux	Enoxaparin
Anemia	19.6%	16.9%
Fever	13.6%	15.4%
Nausea	11.3%	12.2%
Edema	8.7%	8.8%
Constipation	8.5%	10.5%
Rash	7.5%	8.3%
Vomiting	5.9%	6.0%
Insomnia	5.0%	5.4%

Contraindications

Contraindications to therapy with fondaparinux, enoxaparin, and dalteparin are listed in **Table 3, p. 2**.

Dosage

FDA-approved dosages for fondaparinux, enoxaparin, and dalteparin are listed by indication in **Table 4, above**.

Clinical trials

EPHESUS 2000

Lassen et al. Postoperative fondaparinux vs. preoperative and postoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: A randomized double-blind comparison.[10]

- N = 2,309.
- Methods: Patients received fondaparinux 2.5 mg SQ, given a mean of six hours post-operation and continuing once daily for 5-9 days or enoxaparin 40 mg 12 hours before operation and continuing once daily for 5-9 days.
- Primary efficacy outcome: Venous thromboembolism (VTE) up to day 11.
- Primary safety outcomes: Bleeding and death.
- Primary efficacy results: VTE: fondaparinux 4%, enoxaparin 9%. Fondaparinux had a relative risk reduction of 55.9% over enoxaparin ($P < 0.001$).
- Primacy safety results: No fatal bleeding or severe thrombocytopenia was reported in either group.
- Limitations: Twenty-two percent of enoxaparin patients did not receive a preoperative dose as per study protocol.

PENTATHLON 2000

Turpie et al. Postoperative fondaparinux vs. postoperative enoxaparin for prevention of

Table 5. Efficacy results from clinical trials

	Fondaparinux	Enoxaparin	P value	Relative risk reduction
EPHESUS 2000 (hip replacement)				
VTE	37/908 (4%)	85/919 (9%)	<0.0001	-55.9 (-72.8 to -33.1)
Any deep vein thrombosis (DVT)	36/908 (4%)	83/918 (9%)	<0.0001	-56.1 (-73.2 to -32.9)
Proximal DVT	6/922 (0.7%)	23/927 (2%)	0.0021	-73.8 (-95.2 to -24.4
Distal DVT	30/909 (3%)	67/917 (7%)	<0.0001	-54.8 (74.1 to -27.4)
PENTATHLON 2000 (hip replacement)				
VTE	48/787 (6%)	66/797 (8%)	0.099	-26.3 (-52.8 to 10.8)
Distal DVT	34/796 (4%)	54/800 (7%)	0.037	-36.7 (63.1 to 2.4)
Any DVT	44/784 (5.6%)	65/796 (8%)	0.047	-31.3 (-56.8 to -4.8)
PENTAMAKS 1999 (knee replacement)				
VTE	45/361 (12.5%)	101/363 (27.8%)	<0.001	55.2 (-36.2 to -70.2)
Any DVT	45/361 (12.5%)	98/361 (27.1%)	<0.001	54.1 (-34.5 to -69.6)
Distal DVT	35/372 (9.4%)	78/366 (21.3%)	<0.001	55.9 (-33.0 to -72.9)
PENTHIFRA 1999 (hip fracture)				
VTE	52/626 (8.3%)	119/624 (19.1%)	<0.001	56.4 (-39.0 to -70.3)
Any DVT	49/624 (7.9%)	117/623 (18.8%)	<0.001	58.2 (-41.0 to -71.8)
Distal DVT	42/627 (6.7%)	94/626 (15.0%)	<0.001	55.4 (-34.4 to -71.3)

venous thromboembolism after elective hip-replacement surgery: A randomized double-blind comparison.[11]

• N = 1,584.

• Methods: Patients received either fondaparinux 2.5 mg SQ 4-8 hours postoperatively and continuing once daily for 5-9 days or enoxaparin 30 mg SQ 12-24 hours preoperatively and continuing every 12 hours for 5-9 days.

• Primary efficacy outcome: VTE to day 1.

• Primary safety outcome: Bleeding and death.

• Primary efficacy result: VTE: fondaparinux 6%, enoxaparin 8%. Fondaparinux had a statistically insignificant 26.3% relative risk reduction over enoxaparin (P = 0.099).

• Primacy safety result: No fatal bleeding or severe thrombocytopenia was reported in either group. The bleeding index ‡2 was higher in the fondaparinux group (2% fondaparinux vs. 0.7% enoxaparin), but no statistical information was provided.

PENTAMAKS 1999

Bauer et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery.[12]

• N = 1,049.

• Methods: Patients received either fondaparinux 2.5 mg SQ 6 ± 2 hours postoperatively and continuing once daily for 5-9 days or enoxaparin 30 mg SQ 12-24 hours postoperatively and continuing every 12 hours for 5-9 days.

• Primary efficacy outcome: VTE to day 11.

• Primary safety outcome: Bleeding.

• Primary efficacy result: VTE: fondaparinux 12.5%, enoxaparin 27.8%. Fondaparinux had a 55.2% relative risk reduction over enoxaparin (P < 0.001).

• Primacy safety result: The total for the primary safety outcome was 11 major bleedings in the fondaparinux group and one in the enoxaparin group (P = 0.006).

Table 6. Safety results from clinical trials

Primary outcome

Clinical Trials	EPHESUS 2000		PENTATHLON 2000		PENTAMAKS 1999		PENTHIFRA 1999	
	Fondaparinux N=1140	Enoxaparin N=1133	Fondaparinux N=1128	Enoxaparin N=1129	Fondaparinux N=517	Enoxaparin N=517	Fondaparinux N=831	Enoxaparin N=842
Fatal bleeding	0	0	0	0	0	0	0	1 (0.1%)
Bleeding in critical organ	0	0	0	1 (0.1%)	0	0	0	0
Bleeding leading to reoperation	5 (<1%)	3 (<1%)	2 (0.2%)	2 (0.2%)	2 (0.4%)	1 (0.2%)	3 (0.4%)	2 (0.2%)
Bleeding with a bleeding index >2	42 (4%)	29 (3%)	18 (1.6%)	8 (0.7%)	9 (1.7%)	0	15 (1.8%)	16 (1.9%)

Secondary Outcome

Clinical Trials	EPHESUS 2000		PENTATHLON 2000		PENTAMAKS 1999		PENTHIFRA 1999	
	Fondaparinux N=1140	Enoxaparin N=1133	Fondaparinux N=1128	Enoxaparin N=1129	Fondaparinux N=517	Enoxaparin N=517	Fondaparinux N=831	Enoxaparin N=842
Transfusions	714 (63%)	690 (61%)	593 (53%)	555 (49%)	222 (42.9%)	197 (38.1%)	34 (4.1%)	18 (2.1%)
Blood transfusions units among patients transfused for volume replacement	2 (1-10)	2 (1-10)	2 (1-8)	2 (1-9)	1.9 ± 1.1	1.8 ± 0.9	2.7 ± 1.5	2.8 ± 1.8
Death from any cause	0	2 (0-2%)	3 (0.3%)	1 (0.1%)	1 (0.4%)	2 (0.4%)	11 (1.3%)	16 (1.9%)

• Limitations: Enoxaparin had a higher percentage of patients who received discouraged therapy (NSAIDS or ASA; fondaparinux 12.2% vs. 16.5 % enoxaparin).

PENTHIFRA 1999

Eriksson et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip fracture surgery.[13]

• N = 1,673.

• Methods: Patients received either fondaparinux 2.5 mg SQ given 6 ± 2 hours postoperatively and continuing for 5-9 days or enoxaparin 40 mg SQ given 12 ± 2 hours preoperatively and continuing once daily for 5-9 days.

• Primary efficacy outcome: VTE to day 11.

• Primary safety outcomes: Major bleeding and mortality from all causes.

• Primary efficacy result: VTE: fondaparinux 8.3%, enoxaparin 19.1%. Fondaparinux had a 56.4% relative risk reduction over enoxaparin ($P < 0.001$).

• Primary safety result: No statistically significant differences were reported between the two groups in the incidence of death or clinically relevant bleeding.

• Limitations:

— 10.9% of fondaparinux patients received a dose preoperatively.

— 74.4% of enoxaparin patients did not receive the medication preoperatively.

Efficacy, safety, and cost

Comparative efficacy, safety, and cost information is listed in **Table 5, p. 4; Table 6, above; and Table 7, p. 6**.

Conclusions

Fondaparinux sodium appears to be an effective medication for the prophylaxis of DVT in hip fracture, hip replacement, and knee replacement surgeries. However, there are several weaknesses in the trials that may limit their reliability. According to the PENTAMAKS study, the VTE occurrence with enoxaparin is greater than 25%. Historically, this occurrence has been reported as 10%-15%. There was no statistically

significant different in VTE occurrence between fondaparinux and enoxaparin in the PENTATHLON study. Another fondaparinux limitation is its inability to be reversed by protamine, compromising its safety. In the clinical trials, there was a tendency toward more bleeding with fondaparinux, but limited statistical information was provided. This medication also has stringent renal dosing restrictions, as well as a contraindication in those patients with severe renal impairment.

In addition to those limitations mentioned, the manufacturer funded all of the clinical trials. In two of the studies, the authors served as consultants to the company that manufactures fondaparinux. Due to the weaknesses in clinical studies, high cost, its indications being limited to orthopedics only, and the lack of published data to support other indications, fondaparinux should not replace dalteparin as the workhorse for these indications. According to current prices, approximately $150,000-$200,000 will be saved annually if dalteparin is used in 100% of the patients prescribed low molecular weight heparin or fondaparinux. Every time either enoxaparin or fondaparinux is used, it will decrease cost savings. For these reasons, fondaparinux will not be added as a formulary agent at our institution at this time. Fondaparinux may have a place in therapy in the future, but currently, there is not enough reliable information to correlate the relative safety and efficacy of these products.

Table 7. Cost Comparison of fondaparinux and LMWHs DVT prophylaxis for seven days[14,15]

Side effect	Incidence
Eye strain or visual disturbances	19-27%
Headache	13-21%
Agitation or feeling "wired"	6-13%
Nausea	7%
Sweating	7%
Sedation	6-7%

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Do changes in the seasons make some people SAD?

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Many people experience the "winter-time blues." Some people may feel down, have less energy, put on a few pounds, or have difficulty getting out of bed in the mornings during the dark, short days of winter. However, people who have seasonal affective disorder (SAD) experience these same symptoms to the degree that it inhibits their normal daily life. SAD sufferers often feel chronically depressed and fatigued. They also do not want to be socially active and may withdraw from the world. In the United States, about 6% of the population (approximately 10 million people) suffers from SAD. This disorder is predominately found in females and in people 20-30 years of age.

Norman E. Rosenthal, MD, and his research group at the National Institutes of Mental Health first described seasonal affective disorder in 1984. They coined the term SAD to describe a type of depression that varies with the seasons. SAD is characterized by four aspects: recurrent major depressive episodes that start (September-October) and end (March-April) at the same time each year; full remission of symptoms during the unaffected period of the year (May-August); relatively more seasonal depressive episodes than non-seasonal episodes; and depressive episodes occurring for at least two consecutive years. These criteria are used in the fourth edition of the standard psychiatric Diagnostic and Statistical Manual for diagnostic purposes. Also, several instruments are used in the diagnosis of SAD, such as the Seasonal Pattern Assessment Questionnaire, which is a self-report questionnaire that retrospectively assesses the magnitude of seasonal change in sleep, social activity, mood, weight, appetite, and energy. Another instrument that measures the severity of SAD is the Structured Clinical Interview Guide for the Hamilton Depression Rating Scale, SAD version.

The usual symptoms of SAD are depression including low mood, reduced interest, decreased concentration, low energy, and fatigue. SAD sufferers also experience "reverse" or "atypical" vegetative symptoms of depression such as increased sleep, increased appetite, unacceptable weight gain, and carbohydrate/sweets craving.

The etiology and pathophysiology of SAD are unknown. There are three main hypotheses for SAD: the circadian rhythm disturbance, melatonin, and neurotransmitters. The circadian rhythm disturbance hypothesizes that biological rhythms are cyclical variations in biological activities and functions (e.g., physiological function and emotional state). Therefore, an abnormal change in the biological function causes affective illness, which is a disruption of the patient's sleeping patterns, diurnal variation in mood, and seasonal patterns of recurrence. It is thought that the circadian rhythm is linked to the light-dark cycle of the solar day, so that if an individual is unable to adapt to changes, then it may affect his or her well-being.

Another hypothesis involves melatonin, an endogenous hormone that is secreted nocturnally by the pineal gland and is believed to cause symptoms of depression. Melatonin is produced at increased levels in the dark, so when the days are shorter and darker, the production of this hormone increases; however, melatonin production can be suppressed by bright light.

Table 1. Common side effects of light therapy reported in clinical trials

Side effect	Incidence
Eye strain or visual disturbances	19%-27%
Headache	13%-21%
Agitation or feeling "wired"	6%-13%
Nausea	7%
Sweating	7%
Sedation	6%-7%

The third hypothesis involves neurotransmitters such as serotonin. Serotonin is thought to be linked to SAD because it has a distinct seasonal pattern of metabolism in normal humans. The lowest levels of serotonin generally occur in the winter and spring, whereas the highest levels occur in the summer and fall. These three hypotheses have been studied, but none have been proven to explain completely the manifestations of SAD.

There are two main treatments for this disorder: phototherapy and antidepressant drug therapy. There have been more than 60 controlled trials of light therapy in SAD, with most demonstrating effective results. Light therapy involves sitting in front of a light box during the fall and winter months, usually for 30 minutes a day. The usual "dose" of light is 10,000 lux (illuminance).

Table 2. Choosing light therapy or antidepressant drug therapy

Consider light therapy as first-line therapy when:	Consider medications as first-line therapy when:
Less severe depression	More severe depression
Good compliance for light therapy	Low interest or motivation for light therapy
Warrants non-pharmacologic therapy (pregnancy)	Light therapy too inconvenient
Able and willing to make time commitment for light therapy	Unable to make time commitment for light therapy
Contraindications to drug therapy (hepatic disease, allergies)	Contraindications to light therapy (retinal disease, photosensitizing drug)
Intolerant to medication side effects	Intolerant to light therapy side effects
Assessing costs: Greater initial cost but less ongoing cost	Assessing costs: Less initial cost but greater ongoing cost
Assessing costs: Light box covered by insurance?	Assessing costs: Medications covered by insurance?

Response to light therapy usually is seen within two to four days; however, some patients may need light exposure for up to two weeks before seeing an improvement. Even though the side effects of light therapy are rare, the most common side effects reported in the clinical trials are listed in **Table 1, p. 7**.

In clinical trials, the most effective time to receive light therapy is in the early morning, upon awakening. However, some patients may benefit from light therapy at other times during the day. There are no absolute contraindications to light therapy and no evidence that light therapy is associated with ocular or retinal damage.

Antidepressant drug therapy is another treatment for SAD, although there are only two reliable clinical trials supporting this use. The first trial found that sertraline was significantly superior to placebo in regard to clinical response rate and depression scores. The other study found that fluoxetine was significantly superior to placebo in the clinical response rates but not in the depression scores. The usual doses of the antidepressants are the same as those used in other nonseasonal major depressive disorders. Sertraline and fluoxetine are generally well-tolerated. Patients using antidepressant drugs generally demonstrate an improvement in symptoms within three to four weeks. Other antidepressants may be effective in the treatment of SAD but have not been studied.

Most patients are treated only during the symptomatic winter months, and then discontinue their treatments during the spring and summer months. The treatments are then restarted in the autumn. Some patients can wait until they have mild symptoms before restarting treatment; others may opt to start treatment well ahead of their usual onset time (at least two weeks ahead for light therapy and four weeks ahead for antidepressants) to prevent an episode. Because the onset of action of light is rapid, continuous light therapy throughout the summer is not necessary, although some patients occasionally use light therapy for transient, mild symptoms during the summer. Continuous antidepressant treatment (throughout the summer) is indicated in patients who have problems with compliance, take a long time to taper on and off medications, have difficulty dating onset of symptoms in the fall, or have occasional, transient symptoms in the summer.

How do you choose between light therapy and antidepressant drug therapy? Listed in **Table 2, above**, are important factors for patients and physicians to consider when choosing a therapy.

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