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Prescription Drug User Fee Act up for reauthorization

FDA sought input on fees, risk management issues

The Prescription Drug User Fee Act (PDUFA) program is once again up for renewal. Most pharmacy groups will stand behind the program — if a few changes are made.

"It has worked and should be reauthorized, although some improvements would be welcome," says **Susan C. Winckler**, RPh, JD, group director of policy and advocacy for the American Pharmaceutical Association in Washington, DC.

"It is a good thing to reauthorize. It certainly speeded up the drug approval process," says **Gary C. Stein**, PhD, director of federal regulatory affairs for the American Society of Health-System Pharmacists (ASHP) in Bethesda, MD.

In 1992, Congress passed PDUFA, which authorized the U.S. Food and Drug Administration (FDA) to collect fees from companies that produce certain human drug and biological products. Any time a company wants FDA to approve a new drug or biologic prior to marketing, it must submit an application along with a fee to support the review process. In addition, companies pay annual fees for each manufacturing establishment and for each prescription drug product marketed. In 1997, Congress passed the Food and Drug Administration Modernization Act, which included an extension of PDUFA until 2002 (PDUFA II). PDUFA II also expanded the number and type of performance goals that the agency would meet.

The legislative authority for the current PDUFA program, which has significantly reduced median drug approval time, will expire on Sept. 30, 2002. **(For performance statistics of the PDUFA program, see p. 35.)** The president's budget request for fiscal year (FY) 2003 recommends that PDUFA be reauthorized through FY2007. **Tommy G. Thompson**, secretary of the Department of Health and Human Services, announced the plan for PDUFA III March 13. The plan is now ready for consideration by Congress.

Before the plan was finalized, however, FDA asked for input on the current program from health professionals, patient groups, industry, and the general public. On Dec. 7, 2001, FDA held a public meeting to discuss

reauthorization of PDUFA and to solicit stakeholder comments on future PDUFA provisions.

Many of the panelists at this meeting supported inclusion of post-market drug safety surveillance under PDUFA, an activity that currently is prohibited from user fee support. Some panelists also suggested that PDUFA cover increased FDA reviews of direct-to-consumer advertising.

Judy Cahill, CEBS, executive director of the Academy of Managed Care Pharmacy (AMCP) in Alexandria, VA, told FDA that post-marketing surveillance is an essential public health function of FDA because drugs have potential side effects, even when used appropriately. FDA, she said, is in the unique position to aggregate the drug data. She suggested that PDUFA impose a new user fee on manufacturers for the purpose of post-marketing surveillance and that FDA initiate a public awareness campaign aimed at encouraging the reporting of adverse drug events. Lastly, she suggested the possibility of an independent agency to conduct post-marketing surveillance activities.

ASHP also has expressed concern about post-marketing surveillance, Stein says. ASHP wrote FDA a letter on Jan. 25 as a follow-up to the December meeting. In the letter, ASHP strongly encouraged FDA to develop a comprehensive, proactive system for post-marketing surveillance of new drugs that is not dependent on volunteer reporting. This program, ASHP wrote, should include appropriate health professional and consumer education based on findings from the post-marketing surveillance system, and it should be funded through user fees.

The new plan takes note of these concerns, Thompson says. In a statement, he says the new proposal for the program has "significantly expanded resources for risk management activities related to medicines — especially after they enter the marketplace." Stein hasn't seen the proposal, but says he has heard positive comments about changes in the post-marketing surveillance programs.

Avoiding a funding shortfall is another question facing the PDUFA program. Each year, the amount that FDA must spend from appropriations on the drug review process is increased by an inflation factor. Yet since 1992, FDA has not received increased appropriations to cover the costs of the across-the-board pay increases that must be given to all employees.

Also, the fees FDA has collected have been significantly less than expected due to the reduced number of new drug applications and the increased proportion of applications that are exempt from fees. Yet the number of goal-driven tasks for which FDA collects no fees has increased substantially under PDUFA II. "Congress has tended to not give full support to the [PDUFA] appropriations process," Winckler says. "[Congress] has been allowing the user fees to take the place of appropriations. That is not appropriate."

ASHP agrees. "PDUFA fees alone will not completely solve the problems in drug approval and review that are faced by FDA," it said in its letter to the agency. "Lack of appropriate congressional funding for other FDA programs compromises both review quality and drug safety."

Thompson says the funding issue has been tackled in the new proposal, as well. The plan "establishes a financial structure that should put the program on a sound footing for the foreseeable future." ■

HHS proposes changes to federal privacy regulation

Proposal removes patient consent requirements

The Bush administration has proposed changes to the federal privacy rule, to the relief of some pharmacy and hospital advocacy groups.

The proposed changes, announced by the U.S. Department of Health of Human Services (HHS) in March, will "ensure strong privacy protections while correcting unintended consequences that threatened patients' access to quality health care," according to HHS Secretary **Tommy G. Thompson**. The regulations, which were released

Statistics about PDUFA

The Prescription Drug User Fee Act (PDUFA) program has produced significant benefits for public health, says **Lester M. Crawford**, DVM, PhD, deputy commissioner of the U.S. Food and Drug Administration (FDA). His remarks were made before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, on March 6. **(For more information about PDUFA reauthorization, see cover story.)**

The median approval time for priority new drug and biologic applications dropped from 13 months in fiscal year (FY) 1993 to only six months in FY2000, he says. "We do not have complete data for FY2001, but median approval times are projected to remain at six months."

For standard new drug applications, the median approval time was 22 months in FY1993. By FY1999, however, median approval times had declined to 12 months.

During the PDUFA era, FDA reviewers have approved:

- 30 new medicines for cancer;
- 37 new medicines for AIDS;
- 29 medicines to fight infection; and
- 18 medicines for cardiovascular disease.

The pharmaceutical industry also enjoys significant research and development (R&D) savings, Crawford says, as a result of shorter review times. "Each month of reduced review results in an average savings of $2.5 million, or $30 million in R&D cost savings over 12 months. Given that FDA approves an average of 40 NMEs [new molecular entities] and biologics per year, the savings to industry represent $1.2 billion annually. The program represents a bargain in light of the $133 million that industry paid in user fees in FY2001."

Finally, he says, PDUFA also has brought significant benefits for FDA:

- Performance goals have helped streamline and harmonize the management of drug and biological product reviews.
- The program's requirement for comprehensive product reviews and responses has resulted in improvements to the quality of the application review process.

"Most importantly, the fees have enabled the agency to hire additional medical reviewers and other specialists, and upgrade the technology that is essential for the success of the program," says Crawford.

Some critics have argued that speeding up the approval process through PDUFA increases the likelihood that drugs will be pulled off the market. **Susan C. Winckler**, RPh, JD, group director of policy and advocacy for the American Pharmaceutical Association in Washington, DC, disagrees. "The withdrawal of drugs from the market is statistically about the same from before PDUFA to after PDUFA."

That's correct, according to statistics provided by FDA. Before the user fee program passed in the PDUFA, the withdrawal rate was 2.7%. The rate for drugs reviewed under PDUFA (since 1994) is still 2.7%, even though approval times are now about 12 months, compared to 30 months before PDUFA.

Still, Crawford acknowledges in his testimony the risk of bringing new drugs to market that have been tested on a limited population size. "While drugs and biological products are under development, clinical testing is usually limited to small, carefully selected populations of 5,000 or less. After approval, however, millions of patients may be exposed to the drug.

"However, the need to institute a more effective program of risk management for new drugs, and thereby ensure greater patient safety, is clearly warranted by the intrinsic limitations of drug development programs (particularly the size of clinical trials) and the reality that more drugs are launched for the first time in the United States." ■

Dec. 20, 2000, are part of the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. These regulations were designed to limit the nonconsensual use and release of private health information and to give patients rights to access their medical records and to know who has access to them.

The proposed change most likely to affect hospital and health care system pharmacists involves removing the consent requirements for treatment, payment, and health care operations while strengthening requirements for providers to notify patients about their privacy rights and practices. HHS says it had received comments saying that the consent requirements in the current rule interfere with pharmacists filling prescriptions,

referrals made to specialists and hospitals, treatment provided over the telephone, and treatment provided by emergency medical providers. **(For an overview of the proposed changes to the privacy rule, see story, right.)**

In the proposed change, patients would be asked to acknowledge the privacy notice, but doctors and other providers could treat them if they did not. This change would ensure that patients can consider a provider's privacy policies before making health care decisions, but would eliminate barriers to patients' access to care, according to HHS.

"The consent becomes optional so that health care providers could use information for treatment, payment, or health care operations," explains **Susan C. Winckler**, RPh, JD, group director of policy and advocacy for the American Pharmaceutical Association (APhA) in Washington, DC.

"The hospital likely will get a consent," she says. "At a minimum, it will share with the consumer the notice of privacy practices — this is the important part. So consumers do have access to information about how their information will be used. That will likely be done by the hospital for all of the hospital entities, including the pharmacy.

"It's a change that is appropriate and really necessary to have health care continue," Winckler says.

The American Hospital Association (AHA) in Chicago is pleased with the proposed change as well. "Replacing the redundant requirement that patients sign a written consent form for routine uses of their information with a simple but effective written acknowledgement is a common-sense way to enhance patient privacy," writes **Dick Davison**, president of the AHA, in an editorial/opinion article in *USA Today*. AHA has called on 164 lawmakers who advocated changes to the privacy rule last year to reiterate their support to HHS.

Others are not so happy with the proposed change. Sen. **Edward Kennedy** (D-MA) says the administration has "effectively gutted the cornerstone of the medical records privacy regulation" by proposing the change to the consent requirement. "There are few issues of privacy more important than the right to keep information about one's own personal health private." Kennedy, who accuses the Bush administration of putting the interests of corporate America first, intends to hold hearings on the issue and to introduce legislation to reverse this "ill-considered" action.

Privacy groups sounded off, as well. "The elimination of this prior consent requirement strikes at the very heart of the privacy regulation," according to a statement issued by the Health Privacy Project, Georgetown University, Washington, DC. "HHS could have fixed certain unintended consequences of the consent requirements [for example, the impact on filling prescriptions] with more targeted changes, but the department chose instead a more radical and unfortunate approach. This proposal not only eliminates the consent requirement, but it also fails to require that patients acknowledge receipt of the privacy notice."

The American Medical Association (AMA) in Chicago also is concerned that the administration is removing the patient consent requirement instead of modifying it. "If the final privacy rule will be issued without a consent provision, the AMA urges the administration to strictly limit the activities for which patient information could be used without consent," says **Donald J. Palmisano**, MD, JD, AMA's secretary-treasurer. "Right now, patient information can be used without consent for a wide range of business activities, including underwriting, and there is no incentive to de-identify patient records. De-identified medical information should be used whenever possible to best protect patient privacy."

The AMA has been supportive of the idea of the prior written consent in part because in many of their operations, they do secure the prior written consent, Winckler says. "Unfortunately, that reality does not exist for much of the health care system. I have heard their opinion. It's simply one with which we disagree."

The administration is trying to come up with a good solution, and APhA thinks the administration has found one, she continues. "They have actually done a good job in trying to protect the privacy without disrupting care. There are folks who disagree with that. We will see where things go. It is certainly a better proposal than the [current] final regulations." ■

Proposed HHS changes for the privacy rule

The move to eliminate patient consent is generating a lot of controversy, but it was not the only change to the federal privacy regulation proposed by the Department of Health and Human Services (HHS). The proposal would make the following revisions:

- **Strengthen notice provisions and remove**

consent requirements hindering access to care. This change would ensure that patients can consider a provider's privacy policies before making health care decisions, but would eliminate barriers to patients' access to care.

• **Maintain the "minimum necessary" rule, while allowing treatment-related conversations.** As long as a covered entity met the minimum necessary standards and took reasonable safeguards to protect personal health information, incidental disclosures — such as another patient hearing a snippet of conversation — would not be subject to penalties.

• **Assure appropriate parental access to their children's records.**

• **Prohibit use of records for marketing, while allowing appropriate communications.** The proposal would explicitly require covered entities to first obtain specific authorization before sending a patient any marketing materials. At the same time, the proposal would permit doctors and other covered entities to communicate freely with patients about treatment options and other health-related information, including disease-management programs.

The proposal also would make other revisions to simplify the rule's paperwork requirements. It would, for example:

• **Assure privacy, without impeding research.** The proposal would eliminate the need for researchers to use multiple consent forms — one for informed consent to the research and one or more related to information privacy rights.

• **Provide model business associate provisions.** The changes also would give covered entities up to an additional year to change existing contracts, easing the burden of renegotiating contracts all at once.

• **Simplify authorizations.** The changes would allow the use of a single type of authorization form to obtain a patient's permission for a specific use or disclosure that otherwise would not be permitted under the rule.

HHS published information about these proposed changes along with comments and other public input used to develop them in the March 27 *Federal Register*. After reviewing comments from the 30-day comment period, HHS plans to issue a final rule. As it stands now, most covered entities have until April 14, 2003, to comply with the patient privacy rule. The American Pharmaceutical Association (APhA) in Washington, DC, however, has requested that the implementation date be changed.

"You should have a certain period of time to implement the regulations. It is hard to implement them if they are not final," says **Susan C. Winckler**, RPh, JD, APhA's group director of policy and advocacy. They should be coordinated and implemented with federal security standards, as well, she adds. ■

Price differentiation can encourage counterfeiting

FDA reevaluating approach to fake drugs

Hospitals using legitimate sources may rarely encounter counterfeit drugs — but this may change because of the product price differentiation in foreign countries, says one expert.

"The larger the differentiation, the more opportunity there is to counterfeit because the product will be diverted back to this country," says **Marv Shepherd**, PhD, director of the Center for Pharmacoeconomic Studies, College of Pharmacy, University of Texas, Austin. Some of the drugs already counterfeited include epoetin alfa (Epogen), filgrastim (Neupogen), and somatropin (Serostim).

According to the Federal Food, Drug and Cosmetic Act [21 USC Sec. 321(g)], the term "counterfeit drugs" means a drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor.

Counterfeiters can make a counterfeit drug and then sell it directly, Shepherd says. Or they can divert a good product off the market. "Drug diversion has been documented. It's so hard to trace."

He gives an example of how drug diversion works. "I send a million units to South Africa of a drug. They are paying 30 cents a tablet. In this country, the cost is $30 a tablet."

Counterfeiters in South Africa steal the drug and divert it back to this country. "When that happens, they will sell it in the United States — to some wholesaler, retail chain, or hospital system. They may sell it for $10 a tablet."

Meanwhile in South Africa, half the supply is now gone. The supply, however, must meet the requirements of the country. The counterfeiters then dilute the original product. It goes to the next handler of the product within South Africa, and the cycle continues. "They do the same thing. Now you have counterfeit product being introduced again." For hospitals that use legitimate buyers, however, counterfeiters are still not a big problem. "They have been estimated at 5% or less [in the United States]," Shepherd says.

The U.S. Food and Drug Administration (FDA) is taking a new approach to the problem of drug counterfeiting, says **Benjamin L. England**, Esq., regulatory counsel to the Associate Commissioner for Regulatory Affairs.

During June 2000 hearings on the subject, FDA was asked to work more closely with the drug industry in combating counterfeits and to look at ways to assist in authenticating drug products.

After the hearings, the agency reestablished the Counterfeit Drug Working Group, which England had chaired for a number of years. He began talking with representatives of the drug industry as well as representatives in the applied technology industry. "I discovered there was a fair amount of research that has gone into anti-counterfeiting solutions — technology and system design. A lot of brand-protection money was getting poured into [research and development] after the advent of the Internet because many companies, drug industry or not, were getting complaints about their products from markets where they don't sell their products. When they would look at the product in those markets, they would find that the product was counterfeit." The applied technology industry responded and made substantial gains in the area of brand protection.

England and other representatives of the working group concluded that it would make sense for them to put together joint agency/industry working groups. "It would allow us to work more closely with the drug industry with regard to the issue on a more formal basis. Secondly, it would allow us to look at the various options as to how a drug manufacturer or an importer may be able to protect themselves from the risks that counterfeits may pose to the market — and to learn this technology together," England says.

The working groups would look at all the concepts that assist in identifying where a commodity is at any given time and who has access to it, not just at technology applied to a product, he continues. These other concepts include track and trace systems and distribution control.

After the terrorist attacks of Sept. 11, the primary group's focus began to expand into the food arena, as well. The group, therefore, decided to develop at least two working groups, one for foods and one for drugs. "The drug would be at least human and vets, and it may be biologics. We may also break out biologics into a third group."

It didn't take long for the counterfeiting question to get connected to terrorism. Terrorists could tamper with drugs in several ways: infiltrate the manufacturing facility, tamper the product while it is in commerce, or knock it off and introduce it downstream, England says.

Since the Sept. 11 attacks, the general direction of the agency with regard to import programs is being reevaluated, England says. "The counterfeiting is a subset of product security, and product security is a subset of product safety overall. It is an integrated approach." ■

MedDRA 5.0 released

Version 5.0 of the Medical Dictionary for Regulatory Activities (MedDRA) Terminology — the new global standard medical terminology — was released in March.

The International Conference on Harmonisation (ICH) developed MedDRA as a pragmatic, clinically validated medical terminology. The emphasis is on ease-of-use data entry, retrieval, analysis, and display, with a balance between sensitivity and specificity, within the regulatory environment. MedDRA is applicable to all phases of drug development and applicable to the health effects of devices.

MedDRA also is designed to supersede or replace all other terminologies used within the medical product development process. The U.S. Food and Drug Administration already has implemented MedDRA within its Adverse Event Reporting System.

Proponents of MedDRA say that by standardizing medical terminology, it will help speed the exchange of clinical information, facilitate research and safety monitoring, and make the

regulatory approval process more efficient and responsive. MedDRA may not be as user-friendly in the other direction, however, says **Jack Fincham**, PhD, dean and professor of pharmacy practice at the University of Kansas in Lawrence.

The main reason for this is MedDRA's proprietary nature. Realizing that MedDRA would have to be continually maintained and updated, ICH created a Maintenance and Support Services Organization (MSSO) and established as its steering committee trustee the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) in Switzerland. The MSSO reports to IFPMA, and is the only officially authorized provider of MedDRA subscriptions and core services. Health care organizations with tight budgets may not be able to afford the subscriptions, Fincham says.

Along with the updated version of MedDRA, translations of MedDRA to French, German, Portuguese, and Spanish are now available or expected soon. ▼

Americans doubtful about safety of clinical trials

A new Harris Interactive survey finds that only one-third of all adults nationwide are very confident that patients in clinical trials receive very good medical care. The survey says about one-quarter of adults are very confident that new treatments are tested on humans only after there is valid evidence that the treatments are likely to be effective and safe.

The nationwide survey was conducted on-line between Feb. 21 and 27 with a sample of 2,031 adults ages 18 and older. The survey also found that 83% of all adults believe it is "essential" or "very important" that "all new prescription drugs or other new treatments should be tested on human beings in clinical trials before they are approved for general use." African-Americans and Hispanics tended to be most skeptical of the safety and effectiveness of treatments that patients received during clinical trials. The Harris survey results suggest that a major educational campaign is necessary because the need for clinical trial participants is likely to grow rapidly as more, and bigger, trials are planned in the future. For more information, see the health care news section of www.harrisinteractive.com. ▼

FDA posts drug warnings, labeling changes

The Food and Drug Administration (FDA) recently posted warnings on its MedWatch web site about several drugs. They are:

• **FDA and Bristol-Myers Squibb have notified health care providers caring for persons with HIV of the potential for lactic acidosis as a complication of therapy with stavudine (Zerit), d4T.** The early signs and symptoms of clinical events associated with hyperlactatemia should receive careful attention because of the life-threatening potential of the most extreme manifestation, lactic acidosis syndrome.

Bristol-Myers Squibb has received reports of rare occurrences of rapidly ascending neuromuscular weakness, mimicking the clinical presentation of Guillain-Barré syndrome (including

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Editorial Questions

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respiratory failure), in HIV-infected patients receiving stavudine in combination with other antiretrovirals. Some cases were fatal. If motor weakness develops in a patient receiving stavudine, the drug should be discontinued.

For more information, see www.fda.gov/medwatch/SAFETY/2002/safety02.htm#zerit.

• **FDA and Aventis strengthened the Warnings and Precautions sections of the enoxaparin sodium (Lovenox) prescribing information to inform health care professionals that the use of enoxaparin sodium Injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves.** New post-marketing safety information concerning congenital anomalies and non-teratogenic effects on pregnant women and fetuses also is described.

For more information, see www.fda.gov/medwatch/SAFETY/2002/safety02.htm#loveno.

• **The labeling for ziprasidone HCl (Geodon) capsules has been clarified. The revisions, made in consultation with FDA, clarify information that already had been included in the package insert.** The Contraindications section included a list of seven drugs contraindicated with ziprasidone and stated that this list of drugs was "not a complete list." However, not all physicians, pharmacists, and pharmacy databases interpreted this language as intended. Some may have considered certain drugs excluded from the contraindication, while others believed that, irrespective of the level of documentation, any drug associated with QT-prolongation was contraindicated with ziprasidone. Pfizer and FDA agreed there was a need to provide greater clarity around the particular drugs or types of drugs that are contraindicated with Geodon. For more information, see www.fda.gov/medwatch/SAFETY/2002/safety02.htm#geodon. ▼

Study finds heart drug may have serious side effects

A drug often used to treat worsening heart failure in hospitalized patients may cause low blood pressure and abnormal heart rhythms, says a recent study published in the March 27 *Journal of the American Medical Association*.

Mihai Gheorghiade, MD, of Northwestern University in Chicago, told the Associated Press that the findings suggest that the drug, milrinone, should be reserved for patients who do not respond to other medication.

The study is one of the few to compare a placebo with a drug for worsening heart failure. Despite the poor results, it shows that such studies can and should be done on similar drugs, Gheorghiade says.

The study looked at 951 patients admitted with an exacerbation of systolic heart failure not requiring intravenous inotropic support. The patients were randomly assigned to receive either a 48-hour infusion of milrinone or saline placebo. The median number of days hospitalized for cardiovascular causes within 60 days after randomization did not differ significantly between patients given milrinone (6 days) compared with placebo (7 days).

However, sustained hypotension requiring intervention (10.7% vs. 3.2%) and new atrial arrhythmias (4.6% vs. 1.5%) occurred more frequently in patients who received milrinone. The milrinone and placebo groups did not differ significantly in in-hospital mortality (3.8% vs. 2.3%), 60-day mortality (10.3% vs. 8.9%), or the composite incidence of death or readmission (35.0% vs. 35.3%), respectively. ■

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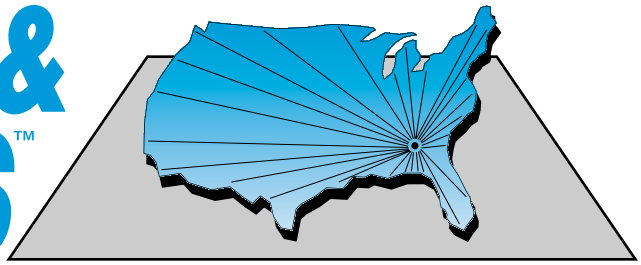

Levobupivacaine (Chirocaine) Formulary Evaluation

By **Elizabeth Butler**, PharmD
Written as a PharmD candidate at McWhorter School of Pharmacy, Samford University, Birmingham, AL

Local anesthetics

Bupivacaine — various manufacturers
Levobupicaine (Chirocaine) — Purdue Pharma L.P.

Mechanism of action

Local anesthetic agents such as levobupivacaine and bupivacaine are amide anesthetics, and they exert their action by affecting voltage-sensitive ion channels on excitable membranes. They potentiate this action by blocking impulse transmission through sodium channels, which occurs in sensory and motor nerves involved in perception and coordination. Hindrance of nerve impulse transmission in these nerves produces decreased muscle control and local anesthesia. Because sodium channels are so abundant in the body, these agents also exert some effects on the central nervous system and on smooth muscle and cardiac muscle. It is this action that contributes to the side effects seen with these agents.

Indications

Levobupivacaine is indicated for the production of local or regional anesthesia for surgery and obstetrics, and for postoperative pain management. In surgical anesthesia, levobupivacaine can be used in an epidural, as a peripheral neural blockade, and for local infiltration. In pain management, levobupivacaine can be used for continuous epidural infusion, intermittent epidural neural blockade, continuous or intermittent peripheral neural blockade, or local infiltration. For continuous epidural analgesia, levobupivacaine can be used in combination with epidural fentanyl or clonidine. Dosage of levobupivacaine should begin with a small test dose and be followed by small increments to produce effective analgesia with the smallest dose possible.

Pharmacokinetics

The pharmacokinetic profiles of levobupivacaine and bupivaine are summarized in **Table 1, below**.[1]

Clinical studies

Management of labor pain. A multicenter, randomized, double-blind, parallel group study of 137 patients comparing levobupivacaine 0.25% and bupivacaine 0.25% for epidural analgesia for labor pain found that levobupivacaine produced similar analgesia rates as bupivacaine.[2,3] In another randomized, double-blind, parallel group study comparing levobupivacaine 0.125% and bupivacaine 0.125%, levobupivacaine was found to exhibit similar efficacy for labor analgesia as bupivacaine.[4] The major limitation of these studies was small sample size; only 80 patients were evaluated in the Kopacz study.[4] The recommended dose of levobupivacaine 0.25%, administered as an intermittent epidural bolus, is 10-20 mL (25-50 mg). In both of these

Table 1. Pharmacokinetic profiles of levobupivacaine and bupivacaine.

Variable	Levobupivacaine	Bupivacaine
Bioavailability	100%	100%
C_{max}	1.445 mcg/mL	1.421 mcg/mL
AUC (in an hour)	1.153 mcg/mL	1.166 mcg/mL
$T_{1/2}$	1.27 hrs	1.15 hrs
V_d	66.91 L	59.97 L
Clearance	39.06 L/hr	38.12 L/hr
Formulation	IV	IV

studies, no major adverse effects were noted, and incidence of mild-to-moderate adverse events was the same between the two medications.

Epidural anesthesia for surgery. A randomized, double-blind, three-arm parallel group study compared the efficacy of two concentrations of levobupivacaine (0.5% and 0.75%) with bupivacaine 0.5%.[5] Levobupivacaine 0.75% produced significantly longer duration of sensory block than did 0.5% levobupivacaine or bupivacaine. Similar efficacy was noted between levobupivacaine 0.5% and bupivacaine 0.5%. The number of patients (n = 57) limited this trial, and the sponsor was the manufacturer of levobupivacaine. Another randomized, double-blind, parallel group study compared levobupivacaine 0.75% to bupivacaine 0.75%. This study found similar efficacy between the two groups.[3]

Management of postoperative pain. A multicenter, randomized, double-blind, three parallel group study compared three concentrations of levobupivacaine for the treatment of postoperative pain.[6] Patients in the levobupivacaine 0.0625% treatment group experienced more postoperative pain than did the patients in the levobupivacaine 0.125% and 0.25% groups. The 0.0625% concentration and the 0.125% concentration are not recommended for use as adjuncts in managing postoperative pain. Another study found levobupivacaine 0.125% to be efficacious as an adjunct when combined with fentanyl or clonidine for the management of postoperative pain.[7,8]

In general, the clinical studies shown here found similar efficacy between levobupivacaine and bupivacaine. The side effect profiles of both medications are similar; however, side effects develop at slightly lower doses of bupivacaine than levobupivacaine. In some cases, this difference was not statistically significant. The adverse effects occurring in these studies were similar between groups, with no major adverse effects occurring in either group.

Levobupivacaine's manufacturer is promoting this difference as the reason to use levobupivacaine instead of bupivacaine. Also, the European manufacturer of levobupivacaine sponsored all the clinical trials mentioned above, and the numbers of patients studied were relatively small.

Adverse effects

The most dangerous side effects of this class of drugs occur with inadvertent intravascular injection. The result may be ventricular tachycardia or ventricular fibrillation. Clinical manifestations of central nervous system (CNS) and cardiac effects include lightheadedness, tinnitus, and numbness of tongue. More serious effects may present as convulsions, decreased cardiac function, potential arrhythmias, and cardiovascular collapse and death. These side effects can occur with both levobupivacaine and bupivacaine. One study tested the effects of levobupivacaine and bupivacaine when injected intravenously in sheep.[9] This study found the mean dose at which seizures occurred was 85 mg for bupivacaine and 103 mg for levobupivacaine. Several sheep died with doses of 125, 150, and 200 mg of bupivacaine; however, no animals died at the same doses of levobupivacaine. It should be noted that these doses are larger than usual doses in epidural anesthesia. Large doses (greater than 100 mg) of both medications caused left ventricular myocardial fiber shortening.[9]

Bupivacaine doses of greater than 75 mg and levobupivacaine doses of greater than 100 mg caused increased heart rate. This increase occurred at lower doses with bupivacaine than with levobupivacaine. Large doses of both medications produced QRS prolongation; however, there was no significant difference between the two medications in this respect. In general, bupivacaine produced more significant arrhythmias than levobupivacaine. The arrhythmias caused by levobupivacaine were transient and caused no permanent sequale.[9] This study had some major limitations including extremely small sample size (only 14 sheep were studied), possible introduction of bias in support of the article, direct intravenous administration, and the fact that the study was performed in sheep. The company that manufactures levobupivacaine in Europe sponsored this article.

Another study evaluated the safety of levobupivacaine and bupivacaine in 14 healthy volunteers.[10] The doses used in this study were between 100 and 200 mg. This study found mild-to-moderate CNS symptoms occurred after intravenous administration in all participants with both medications. Both drugs produced slight increases in the PR and QTc intervals, but the differences between the two drugs were not statistically significant.

Bupivacaine caused a greater decrease in stroke index, acceleration index, and ejection fraction than did levobupivacaine.[10] This indicates that levobupivacaine may be used as an

alternative drug in patients needing high doses of local anesthetics. This study also has several limitations including small sample size and inclusion of healthy subjects. The manufacturer of levobupivacaine sponsored the trial.

It is important to remember that all the studies regarding safety of these medications were conducted with intravenous administration. These medications are approved only for epidural or local use.

Bupivacaine is classified as pregnancy category C, and levobupivacaine is classified as category B. These two drugs will be administered most frequently near delivery time in pregnancy situations.

Drug interactions

Levobupivacaine should be used with caution in patients who are receiving other local anesthetics or agents structurally related to amide-type local anesthetics. The metabolism of levobupivacaine could be affected by known CYP3A4 inducers such as phenytoin, phenobarbital, and rifampin, and by CYP3A4 inhibitors such as ketoconazole, protease inhibitors, erythromycin, and verapamil. No drug interactions have been reported; however, these mentioned medications have the potential to interact with levobupivacaine.

Cost

If levobupivacaine replaced bupivacaine on the formulary, and usage in the next year is comparable to the past 12 months usage, the additional cost to the hospital for levobupivacaine would be about $45,000/yr. For more pricing information, **see Table 2, right**.[11]

Summary and recommendations

According to the data presently available, including clinical trials, both levobupivacaine and bupivacaine demonstrate approximately the same efficacy and safety. Bupivacaine is available as generic and levobupivacaine is not. This would present a large cost difference. Because of the similarity between the two drugs, it is difficult to select one over the other in terms of efficacy. Safety is a concern with patients who require high doses of local anesthetics, and in patients with high cardiac risk. The differences in safety between levobupivacaine and bupivacaine are not significant enough to warrant the use of levobupivacaine exclusively.

An important factor to explore is the cost to the hospital of a complete change to levobupivacaine. If levobupivacaine must be added to the formulary, then criteria for use should be established and each patient should meet these criteria before levobupivacaine is dispensed. Some examples of possible inclusion criteria for levobupivacaine use include the use of high doses of anesthetics, increased cardiovascular risk of developing arrhythmias, and pregnant women at increased risk of developing cardiac complications.

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Table 2. Pricing information.

Drug	*Cost per unit*
Sensorcaine-MPF (bupivacaine)	
10 mL single-dose vial	
0.25%	$1.44
0.5%	$1.54
0.75%	$1.75
30 mL single-dose vial	
0.25%	$1.26
0.5%	$1.35
0.75%	$2.87
Levobupivacaine	
10 mL single-dose vial	
0.25%	$5.30
0.5%	$5.71
0.75%	$6.71
30 mL single-dose vial	
0.25%	$5.92
0.5%	$6.57
0.75%	$9.67

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Drug interactions with thyroid drugs

By **Melissa Headrick**, PharmD
Written as a PharmD candidate at Auburn University School of Pharmacy, Auburn, AL

Thyroid-replacement medications, such as levothyroxine (Synthroid, Levoxyl), are used to treat a variety of medical conditions. The most common is hypothyroidism, but these agents also can be used to suppress pituitary thyroid-stimulating hormone (TSH) and for diagnostic purposes. The optimal dose for hypothyroidism should be the minimum that restores normal serum TSH levels. The average maintenance dosage is 75-125 mcg/d orally, but dosages vary among patients and indications.

Many drug classes and individual drugs can interact with thyroid hormones by several different mechanisms. The most common interactions are with prescription agents, such as rifampin, anticonvulsants, certain antacids, warfarin, and digoxin.

In addition to the prescription agents that are detailed in the Table **(see p. 5)**, over-the-counter agents and herbal products have been reported to interact with thyroid hormones. Ferrous sulfate has been shown to reduce thyroid hormone serum levels and therapeutic response. Patients need to be educated to separate the administration of iron salts from the thyroid hormone by as much time as possible. Soy also has been shown to decrease the effectiveness of thyroid hormones. The mechanism is thought to involve impaired absorption and enterohepatic circulation of thyroid hormones, resulting in significant fecal loss of the drug. Patients should avoid taking soy supplements while taking thyroid medications. Two herbal products, bugleweed and lemon balm, also have been reported to interfere with the action of thyroid hormones and thus should not be used by these patients.

If a patient taking thyroid hormone experiences symptoms of hyperthyroidism (tachycardia, warm skin, nervousness, weight loss, insomnia) or hypothyroidism (facial swelling, cold intolerance, dry skin, weight gain), a drug interaction could be occurring. Some possible management options include changing the dose of thyroid hormone, monitoring TSH levels, and separating the interacting agents. Clinical judgment should be used to evaluate these and other drugs for their potential to interact with thyroid hormones.

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Table. Effects on thyroid-stimulating hormone

Drug name	Effect	Management
Anti-infective agents		
Rifampin	Increased rate of thyroid hormone metabolism; decreased thyroid hormone effectiveness by increased metabolism of thyroid hormone. Often a clinically significant reaction when rifampin is given to a patient who is stable on thyroid.	Monitor TSH; may need to increase dose of thyroid hormone.
Chloroquine	Increased TSH; decreased thyroid hormone effectiveness by increased metabolism of thyroid hormone. Rarely reported.	Monitor TSH when beginning and ending chloroquine therapy.
Ritonavir	Induction of glucuronyl transferases by ritonavir; decreased thyroid hormone effectiveness. Little clinical evidence available.	Monitor TSH levels. May need to increase dose of thyroid hormone when starting ritonavir.
Anticonvulsants, sedatives/hypnotics		
Carbamazepine	Increased thyroid hormone metabolism. Often a clinically significant reaction when carbamazepine is given to a patient who is stable on thyroid.	Monitor TSH levels and patient response.
Phenobarbital	Increased thyroid hormone metabolism. Often a clinically significant reaction when phenobarbital is given to a patient who is stable on thyroid.	Monitor TSH levels and patient response.
Phenytoin	Increased thyroid hormone metabolism; may displace thyroid hormone from plasma protein-binding sites. Often a clinically significant reaction.	Monitor TSH levels and patient response.
Cardiovascular drugs		
Digitalis glycosides	Decreased digoxin levels when hypothyroid patient becomes euthyroid on thyroid hormone therapy. Rarely reported.	Monitor digoxin levels and heart rate.
Beta blockers	Decreased beta-blocker action when hypothyroid patient becomes euthyroid on thyroid hormone therapy. Little clinical evidence available.	Monitor blood pressure, heart rate, and patient response.
Antihyperlipidemic agents		
Resins: Colestipol, Cholestyramine	Decreased gastrointestinal absorption of thyroid hormone. Little clinical evidence available.	Dose thyroid hormones one hour before or six hours after resin.
Lovastatin	May inhibit the absorption or increase the clearance of thyroid hormones; may increase or decrease the effectiveness of thyroid hormones. Rarely reported. Effect of other statins is unknown.	Monitor TSH levels because reactions are unpredictable.
Clofibrate	Increased levels of serum thyroid-binding globulins. Rarely reported.	Monitor TSH levels.
Gastrointestinal agents		
Aluminum hydroxide antacids	Decreased effect of thyroid hormones because aluminum binds to the thyroid hormone in the gut and decreases absorption. Rarely reported.	Avoid these products if possible; separation of the two products may not be beneficial enough.
Calcium carbonate antacids	Decreased effect of thyroid hormones due to formation of an insoluble chelate to calcium carbonate. Rarely reported.	Separate the drugs by at least four hours.
Sucralfate	Decreased gastrointestinal absorption of thyroid hormones. Little clinical evidence available.	Monitor TSH levels; separate drugs by two hours or use alternative to sucralfate.
Miscellaneous		
Tricyclic antidepressants	Concurrent use may increase therapeutic and toxic effects of both drugs, possibly due to increased catecholamine receptor sensitivity. Onset of tricyclics may be accelerated. Rarely reported.	Monitor TSH levels; monitor patient response to tricyclics.
Estrogen products	Increased serum thyroxine-binding globulin. Little clinical evidence available.	May need to increase thyroid hormone dose if estrogens are given.
Warfarin	Increased metabolism of vitamin K-dependent clotting factors. Often a clinically significant reaction when titrating thyroid therapy.	Monitor international normalized ratio (INR) when initiating or changing dose of thyroid hormone. Less incidence in euthyroid patient.

Drug interactions with birth control pills

By **Monique D. Letson**, PharmD
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Oral contraceptives (OCs) are one of the most widely prescribed classes of drugs in the world and the most commonly prescribed medication for young women. Multiple formulations are available, varying in both the composition of steroid hormones and the dose of each agent. The most frequently prescribed are composed of both an estrogen — most commonly ethinyl estradiol (EE) — and one of a number of progestins. The estrogen content of current preparations ranges from 20 to 50 mcg, with the majority containing 30-35 ug. Preparations with less than 35 mcg of estrogen are referred to as "low-dose" OCs.

Both estrogen and progestin undergo intestinal absorption and metabolism, hepatic metabolism, and enterohepatic recycling. Therefore, both are susceptible to drug interactions with hepatic enzyme-inducing drugs. If patients experience spotting or breakthrough bleeding while taking an OC, it is possible they are experiencing a drug interaction and loss of contraceptive efficacy. OCs with a higher dose of estrogen ($\geq$ 50 mcg) and/or an alternative method (nonhormonal) of birth control may be necessary to protect against unwanted pregnancy.

Although the lists of interactions in Tables 1 and 2 are not absolute, it is important to keep them in mind and warn patients about the possibility when necessary. In addition, because of the unpredictable

Table 1. Drugs that alter oral contraceptive concentrations/ effects.

Drug class	Generic (trade)	Effect	Recommendation
Antibiotics	erythromycin (E-Mycin, etc.) griseofulvin (Grifulvin, etc.) penicillins rifampin (Rifadin, etc.) tetracycline (Sumycin, etc.) ***Risk is present with all antiobiotics.***	Antibiotics disrupt normal GI flora, interfering with enterohepatic recirculation and decreasing OC serum levels and efficacy. Rifampin and griseofulvin also increase OC metabolism by inducing CYP450 enzymes.	Use alternative method of contraception during the antibiotic treatment course and for at least one OC cycle after finishing the antibiotic.
Anticonvulsants	carbamazepine (Tegretol) phenobarbital phenytoin (Dilantin) primidone (Mysoline)	OC action may be decreased. These agents induce CYP450 enzymes, increasing OC metabolism and decreasing OC serum levels.*	Use alternative method of contraception or consider a higher-dose ($\geq$ 50 mcg EE) OC product.
Azole antifungal agents	fluconazole (Diflucan) itraconazole (Sporanox) ketoconazole (Nizoral)	OC action may be decreased.	Use alternative method of contraception during use and for one OC cycle after.
Agents that inhibit estrogen metabolism	grapefruit (or juice) cimetadine (Tagamet) atorvastatin (Lipitor)	Decrease estrogen metabolism, thus increasing estrogen levels and estrogen-related side effects.	Monitor for signs of estrogen excess.

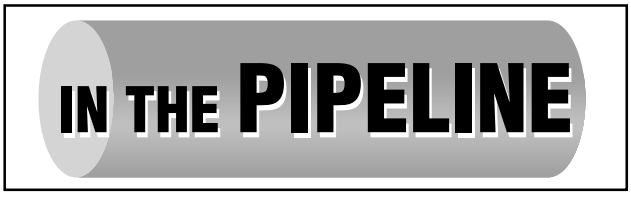
** Other CYP450 enzyme inducers include: pioglitazone (Avadnia); modafinil (Provagil); and anti-retrovirals (protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and St. John's wort).*

Table 2. Drugs altered by co-administration with oral contraceptives.

Drug class	Generic (trade)	Effect	Recommendation
Antidepressants	amitriptyline (Elavil) tricyclic antidepressants imipramine (Tofranil) tricyclic antidepressants selegiline (Eldepryl) monoamine oxides inhibitors	The metabolism of these drugs may be decreased, causing increased concentrations and side effects.	Monitor levels and for signs of toxicity. Decrease antidepressant dose if needed.
Benzodiazepines (BZD)	chlordiazepoxide (Librium) diazepam (Valium) others metabolized by oxidation	BZD metabolism (those oxidized) may be inhibited, increasing their central nervous system effects.	May be necessary to decrease the BZD dose.
Bronchodilator	theophylline (Theo-Dur, etc.)	Metabolism of theophylline may be decreased, increasing theophylline concentrations and side effects.	Monitor theophylline levels when starting or stopping an OC and adjust the dose as needed.
Corticosteroids	hydrocortisone methylprednisolone (Medrol) prednisolone (Delta-Cortef) prednisone (Deltasone)	Metabolism of corticosteroid may be decreased, causing increased concentrations and possible side effects.	Monitor response for several weeks after starting/stopping the OC. Adjust corticosteroid as needed.
Immunosuppressant	cyclosporine (Sandimmune, Neoral)	Estrogens may inhibit metabolism of cyclosporine, causing increased levels and possible toxic levels.	Evaluate cyclosporine levels regularly and adjust as necessary.
Thyroid hormone	levothyroxine (Synthroid)	Estrogens increase thyroxine-binding globulin, possibly decreasing response to thyroid hormone supplementation as a result.	Adjust thyroid therapy as needed (not generally significant in euthyroid patients).

nature of these interactions, the most conservative action should always be taken to avoid the risk of an unwanted pregnancy, adverse effects due to increased drug concentrations, or subtherapeutic pharmacologic effects.

These lists are not intended to be comprehensive listings of drug interactions with oral contraceptive products. Similar drugs not listed that are from the same drug class and are pharmacologically similar also may produce the same interaction with OCs. ■



• Xcyte Therapies has initiated a Phase I/II clinical trial evaluating the use of its Xcellerated T Cells in patients with **hormone-refractory prostate cancer**.

• Protein Design Labs has initiated a Phase II

clinical study to evaluate its humanized antibody visilizumab (Nuvion) in patients with steroid-resistant, acute **graft-versus-host disease**, a potentially fatal complication of hematopoietic cell transplantation.

• Versicor has started a Phase II clinical trial with dalbavancin for the treatment of **catheter-related bloodstream infections**. Dalbavancin is being developed as the first once-weekly treatment for Staphylococcal (Staph) and other serious Gram-positive hospital infections.

• Amylin Pharmaceuticals has initiated the third of three planned Phase III trials of AC2993 (synthetic exendin-4), a compound being studied as a potential treatment for people with **Type 2 diabetes**. This study will evaluate the ability of AC2993 to improve glucose control in people with Type 2 diabetes who currently are not achieving target blood glucose levels with a combination of metformin and sulfonylureas.

• Isis Pharmaceuticals has initiated a Phase II clinical trial of ISIS 104838, an antisense inhibitor of tumor necrosis factor-alpha (TNF-alpha), in **rheumatoid arthritis**.

• Keryx Biopharmaceuticals has begun initial dosing of patients in the Phase II clinical trial of the investigational drug candidate sulodexide (KRX-101) for the treatment of **Human Immunodeficiency Virus Associated Nephropathy** (HIVAN) in AIDS patients.

• Atrix Laboratories has commenced Phase II clinical trials for a proprietary formulation of a low-dose oral interferon-alpha product for the treatment of **oral warts caused by human papilloma virus** (HPV) in HIV-infected patients.

• HepaSense, Ltd., a joint venture of Isis Pharmaceuticals and Elan Corporation has initiated a Phase II clinical trial of ISIS 14803 in patients with chronic **hepatitis C virus infections**.

• Coley Pharmaceutical Group has initiated a multi-center, Phase I clinical study of its lead product candidate, CpG 7909, in combination with Rituxan, an approved monoclonal antibody product. This dose escalation study will assess the safety and tolerability of CpG 7909 in combination with Rituxan in patients with **relapsed or refractory non-Hodgkin's lymphoma**.

• Xcyte Therapies has initiated a Phase I/II clinical trial evaluating the use of its Xcellerated T Cells in patients with **hormone-refractory prostate cancer**.

• Pharmaceuticals has announced that enrollment has begun in a third Phase III clinical trial of INS365 Ophthalmic for **dry eye**.

• The Sydney Melanoma Unit of The University of Sydney's Sydney Cancer Centre plans to proceed with a Phase III study of the Delcath drug delivery system for **inoperable cancer in the liver**, pending approval of the hospital's Institutional Ethics committee.

New FDA Approvals

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

• *Morphine sulfate extended-release by Elan Corp.* The FDA has granted marketing approval of morphine sulfate extended-release (Avinza) capsules for the once-daily treatment of **chronic, moderate-to-severe pain** in patients who require continuous, around-the-clock therapy for an extended period of time.

• *Desloratadine (Clarinex) by Schering-Plough.* In February 2002, desloratadine tablets were approved for the treatment of **perennial allergic rhinitis** and for symptomatic relief of **chronic idiopathic urticaria** in adults and children age 12 and older. Desloratadine, in an oral tablet formulation, was approved for the treatment of seasonal allergic rhinitis in adults and children age 12 and older in December 2001. Desloratadine is a once-daily nonsedating antihistamine that provides 24-hour relief.

• *Nitisinone (Orfadin) by Orphan Pharmaceuticals.* The FDA has approved Orfadin (nitisinone) capsules for the treatment of **hereditary tyrosinemia type I**. Orfadin capsules are to be used in conjunction with a diet restricted in tyrosine and phenylalanine.

• *Neulasta (pegfilgrastim) by Amgen*. Neulasta (pegfilgrastim) is approved as a treatment for patients undergoing chemotherapy, to decrease the incidence of infection by **febrile neutropenia**. It is administered in a single fixed dose with each cycle of chemotherapy.

• *Leuprolide acetate (Eligard) by Atrix Laboratories*. The FDA has approved leuprolide acetate (Eligard) 7.5 mg (formerly Leuprogel One-Month Depot) for the treatment of **advanced prostate cancer**. Eligard (for subcutaneous injection) is designed to deliver 7.5 mg of leuprolide acetate at a controlled rate over a one-month therapeutic period. ■