

Drugs & Therapy

B ♦ U ♦ L ♦ L ♦ E ♦ T ♦ I ♦ N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met on September 16, 2003. 1 drug was added in the *Formulary*. No drugs were deleted, but 2 dosage forms were designated not available and 1 drug was evaluated, but not added.

◆ ADDED

Bupropion Extended-Release
(Wellbutrin® SR by
GlaxoSmithKline)

◆ DELETED

None

◆ NONFORMULARY AND NOT AVAILABLE

Bupropion Extended-Release
(Wellbutrin® XL by
GlaxoSmithKline)

Bupropion Extended-Release
(Zyban® by GlaxoSmithKline)

◆ EVALUATED, BUT NOT ADDED

Omalizumab
(Xolair® by Genentech)*

*Nonformulary use restricted to pharmacy administrative approval.

The **Wellbutrin® SR** dosage form of **bupropion extended-release** was added in the *Formulary*, while the **Wellbutrin® XL** and **Zyban®** versions were designated nonformulary and not available. Wellbutrin® SR is a frequently requested nonformulary drug. Zyban® is occasionally requested through the nonformulary process. Zyban® orders will be automatically changed to bupropion extended-release (eg, Wellbutrin® SR). Wellbutrin® XL was recently approved by the FDA, and it will
(continued on next page)

NATIONAL PHARMACY WEEK IS OCTOBER 20 – 24TH

POLICIES AND PROCEDURES

High-cost and problem-prone drugs

The formulary system attempts to control high-cost and problem-prone drugs before inappropriate use of these agents begins. The formulary determines whether a drug is available, then either provides criteria for use or restricts a drug's availability. Restrictions could include requiring approval by a medical service or limitations by easily identifiable patient characteristics (eg, age). Restrictions could limit use by location (eg, ICU only) or by service (eg, Oncology).

Despite these efforts, the inappropriate use of some problem-prone or high-cost drugs is identified after they have been listed in the *Formulary*. Often these problems are recognized by medication use evaluations, adverse event reports, or by financial data. It is much easier to prevent problems than change inappropriate use after it has begun.

Therefore, the P&T Committee will be using a new procedure when these problems have been identified.

Appropriate use will be established using the following steps.

- The P&T Committee will identify and define the issues that need to be reviewed. Key stakeholders will be identified.
- A letter will be sent to the impacted users of the drug(s) affected asking for science to support their use of the agent.
- A deadline will be established for the submission of the supporting information.
- The submitted data will be combined with an independent evidence-based evaluation of the literature, and an executive summary of the data will be created with recommendations for action.
- The summary and recommendations will be reviewed by an ad hoc committee, which will make a final recommendation to the P&T Committee.

- The final written report and executive summary will be sent back to the impacted users and interested parties prior to this issue being addressed at the P&T Committee.
 - The interested parties will be invited to the P&T Committee meeting when the issue will be discussed to allow these parties to present their points of view.
 - The P&T Committee will make a final decision regarding the appropriate use. This could include restrictions ranging from limiting use to specific indications, limiting doses or dosages, limiting duration of therapy, etc., and specification of who will oversee enforcement of any restrictions.
 - Clinical pharmacists will be used as the first-line for approving use according to the approved criteria.
 - The P&T Committee Chair or designee will provide back-up if there is disagreement on the interpretation of the criteria by the clinical pharmacists.
 - All subsequent use of a drug, which does not meet approved criteria, will be considered experimental and development of a protocol with IRB approval and free drug provided by the sponsor will be the appropriate option for continued use.
 - Re-review of the issue can be requested if new science becomes available.
- The role of the Resource Utilization Committee (RUC) will be to assure that this procedure is appropriately followed.

◆ INSIDE THIS ISSUE

- ◆ No reimbursement
- ◆ Restricted distribution
- ◆ Order review

Formulary update, from page 1 not be available unless new data are submitted to the P&T Committee to justify its use.

Wellbutrin® XL is a once-daily version of bupropion. Wellbutrin® SR and Zyban® are usually given twice a day. Bupropion immediate-release tablets are usually given 3 times a day.

Bupropion immediate-release tablets have been listed in the *Formulary* for many years. Bupropion is a norepinephrine and dopamine reuptake inhibitor that does not affect serotonergic function. It has been marketed in the United States for the treatment of major depression and as therapy for smoking cessation since December 1996. It has also been used for several other off-labeled indications (eg, neuropathic pain).

While unusual, the chemical entity “bupropion extended-release” has been marketed under 2 distinct brand names for a few years. Wellbutrin® SR has labeled indications for the treatment of both depression and smoking cessation, and Zyban has the labeled indication for treatment of smoking cessation only. Zyban® is used only for 7 to 12 weeks.

Clinical studies have established that the efficacy of bupropion SR is similar to other antidepressants for the treatment of depression, although bupropion SR is associated with fewer common adverse effects.

Disadvantages of the immediate-release form of bupropion (bupropion IR) include the concern about seizure risk at higher doses and the need to administer bupropion IR 3-times-a-day. The development of sustained-release formulations allows for once-

or twice-daily administration (and potentially a lower risk of seizures). In addition, the administration of bupropion sustained-release allows for plasma concentration levels that lack some of the more extreme peaks and trough levels that characterize bupropion immediate-release.

The manufacturer of Wellbutrin® SR will lose exclusive rights to this drug within the next 6 to 8 months. A generic version should become available around this time. Generic versions of the drug will be available at a reduced cost.

There is currently no data to support any advantage for the use of a once-daily versus a twice-daily version of bupropion. Systematic reviews of compliance data show that there is little difference in compliance between once-daily and twice-daily administered drugs. The similarity of the brand names of Wellbutrin® SR and Wellbutrin® XL can also lead to dosage errors. Prescribers should carefully assess which of these products their patients are receiving in the outpatient setting.

Omalizumab is a monoclonal antibody directed against IgE. It is an “add-on” therapy for the treatment of allergic asthma in patients who have not received an adequate response to inhaled corticosteroids.

Omalizumab is administered every 2 or 4 weeks by slow subcutaneous injection. It is administered in a physician's office or clinic.

The addition of omalizumab to patients' drug regimens reduced the frequency of allergic asthma exacerbations compared with placebo in clinical trials. More patients treated with omalizumab were able to reduce or discontinue the use of inhaled corti-

costeroids. There is some evidence suggesting omalizumab will decrease the incidence of clinic visits for asthma exacerbations, emergency department visits, and hospitalizations. However, since omalizumab is administered in a clinic, the overall number of clinic visits is expected to rise with this drug.

Adverse reactions are few, but the ultimate safety of this drug is unknown. However, injection site reactions are common. There was a higher incidence of cancer in patients treated with omalizumab during the clinical trials. The FDA has mandated a post-marketing surveillance study, which will not be completed for several years, to examine this issue.

Omalizumab is estimated to cost \$10,000 per year and approximately \$500 per dose. It is available only through a limited distribution network. It can be obtained for inpatient use without a lot of paperwork, but it would be irrational to begin this therapy in the inpatient setting without knowing whether a patient qualifies for the outpatient program.

It is anticipated that few patients will be treated with omalizumab in the outpatient setting. There should be even fewer circumstances where omalizumab should need to be administered in the inpatient setting. Therefore, omalizumab remains nonformulary and will be obtained only with pharmacy administration's approval. It will be approved only for patients with allergic asthma whose routine dosage is due and whose hospital stays will be prolonged. A delay of a few days should not be a problem for the routine administration of omalizumab.

POLICIES AND PROCEDURES

Drugs with no outpatient reimbursement codes

New drugs approved by the FDA for use in outpatient clinics can be problematic for hospital-based clinics, like the Shands-managed clinics. A hospital-based clinic cannot receive reimbursement for these agents until Medicare establishes a reimbursement code. Therefore, these drugs cannot be administered in Shands-operated clinics. Further, it is important that patients not be admitted to the hospital just to avoid the problem with outpatient reimbursement. Inpatient reimbursement will not cover the costs of these agents.

Ironically, physician-run clinics can receive reimbursement for these new agents. One option is to refer patients to community physicians; however,

this could erode the referral base of the treating services. Therefore, it is important to enable the administration of these agents in the University-operated clinics when it is feasible. This will be facilitated by cooperation between Shands clinics and UF clinics.

This issue originally arose when bortezomib (Velcade®) became available. It is very expensive (ie, ~\$20,000 for a course of therapy) and there is no other therapeutic option for refractory multiple myeloma. This is the first time there was no alternative for a new, expensive agent that could not be administered in a hospital-operated clinic. In this particular case, administration in the UF Clinics will be facilitated.

As new agents are approved, the following policy will be used to handle these agents. Drugs with no “pass-through” reimbursement for hospital-based clinics from the Centers for Medicaid and Medicare Services (CMS) will be considered nonformulary and not available for inpatient or outpatient care at Shands at UF. The P&T Committee will approve exceptions. Prescribers can request a review of these agents.

Manufacturers' restricted distribution systems

What do you mean I can't get that medication here? This is a question prescribers are asking more and more.

More than ever, pharmaceutical manufacturers are limiting access to prescription drugs by implementing restricted drug distribution programs. These restricted programs limit the availability of certain drugs, making them obtainable only after specific requirements have been met. Sometimes hospitals cannot obtain restricted drugs under any circumstance. This strategy has been designed to address patient safety issues, cost, and availability associated with some drugs.

Medication safety is well-recognized as a national public health issue. Pressure has been placed on the FDA to ensure safe use of drugs (especially for off-labeled uses) and to regulate supply problems.¹ Although the FDA does not have legal authority to control the practice of medicine or pharmacy, the agency can use its power to encourage certain actions by manufacturers related to drug distribution.

FDA's recent efforts to influence prescribing practices were provoked by its approval of thalidomide. When thalidomide was introduced to the US market in 1998, there was strong public concern about the severe risks associated with its use.² Thalidomide was first marketed in Europe in the 1950s as a sedative. Unfortunately, it was prescribed for nausea and insomnia in pregnant women. Thalidomide's use in pregnant women was associated with severe birth defects. When the FDA approved this medication in the US, the agency imposed a variety of strict regulations governing its use (eg, restricted distribution requiring pregnancy testing). Developing a remedy to the special safety issues of thalidomide essentially became a template for the FDA to pursue tighter restrictions on other drugs.

Remodulin®, a drug used to treat pulmonary hypertension, costs nearly \$100,000 per year. To obtain some extremely expensive drugs, patients must be financially qualified by the distributors of the

drug. This assures that the patient will be able to continue receiving treatment after they have been discharged from the hospital. This generally requires that the patient submit financial information (eg, proof of insurance) and completed paperwork. Both the physician and the patient must be aware of the financial issues and potential problems obtaining the drug. It is important to determine whether the patient will be able to meet their financial obligations.

Some drugs are available only in limited quantities. Thus, patients must be registered in order to obtain drug from the limited supply. This is the case for the injectable drug Fuzeon®, which is used to treat resistant HIV infections. The restricted distribution program for Fuzeon® helps manage the limited supply so it is available for the maximum number of people. Again, this program requires specific paperwork be completed before a patient can receive the drug.

While restricted distribution programs have good intentions, they have introduced increased burdens for patients, practitioners, and manufacturers.^{1,2} From the patient's perspective, restricted distribution programs limit their treatment options. For example, if a medication is dispensed only at certain pharmacies, patients may have difficulty obtaining the product. This could delay access to a drug. Additionally, such programs could influence patients to obtain their drugs from multiple pharmacies. When a patient does not receive all of his or her drugs from the same provider, screening for interactions or adverse effects may not be effective. Also, programs that require the use of informed consent forms or patient registries raise the issue of patient privacy.²

So what does this mean for the prescriber? As a practitioner, it is

important to become familiar with the variety of regulations for each specific product. By completing the requirements involved in obtaining a restricted drug for your patients, you can provide valuable therapeutic options. The table below lists some of the drugs that are currently available through restricted distribution programs and where to find additional information about them.

Not all pharmacies or hospitals are authorized to dispense these drugs, so it is necessary for patients to understand the personal responsibility they must assume. Patients should be instructed to carry an emergency supply of any "life-saving drug" with them at all times. At Shands at UF, only a few drugs listed in the table are available for inpatient use. Xolair®, (nonformulary), Remodulin®, Thalomid®, and Tikosyn®, can be ordered for use at Shands, but there are specific restrictions requiring approval for their use. The remaining drugs in the table must be supplied by the patient if they are to continue therapy while in the hospital. This means that if a patient is currently being treated with Tracleer®, for pulmonary hypertension, or Fuzeon®, for acquired immunodeficiency syndrome, for example, the patient must bring their own drugs from home to use in the hospital.

Restricted drug distribution programs have been implemented to ensure medication safety. However, they have introduced an increased amount of burden and accountability for both health care practitioners and patients.

by Jennifer Norberg, PharmD

REFERENCES

1. Gabay MP. Restricted drug distribution programs. *Am J Health-Syst Pharm.* 2003;60:1525-30.
2. Kracov DA. Legal issues and impact of restricted access and distribution. *J Am Pharm Assoc.* 2001;41(6, suppl 1):S11-5.

DRUG

ADDITIONAL INFORMATION

alosetron (Lotronex®)	1-888-825-5249 or www.lotronex.com
sodium oxybate (Xyrem®)	1-866-Xyrem-88 or www.fda.gov/cder/drug/infopage/xyrem/default.htm
thalidomide (Thalomid®)	1-888-423-5436 or www.celgene.com/steps/index.htm
trovafloxacin (Trovan®)	www.fda.gov/cder/news/trovan/qa.htm
interferon gamma-1b (Actimmune®)	1-877-305-7704 or www.actimmune.com
clozapine (Clozaril®)	1-800-448-5938 or www.clozaril.com
cisapride (Propulsid®)	1-877-795-4247 or www.fda.gov/medwatch/safety/2000/propul1.htm
bosentan (Tracleer®)	www.tracleer.com
treprostnil (Remodulin®)	www.remodulin.com
dofetilide (Tikosyn®)	www.tikosyn.com
enfuvirtide (Fuzeon®)	www.fuzeon.com
alpha-1-proteinase inhibitor (Prolastin®)	www.bayerdirect.com/prod_prol_faq.asp
omalizumab (Xolair®)	https://www.spoconline.com/spoconline/xolair/professionals/welcome.jsp

This publication is produced by the Drug Information and Pharmacy Resource Center under the direction of the Department of Pharmacy Services and the Pharmacy and Therapeutics Committee.

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EDITING, DESIGN, & PRODUCTION

Shands HealthCare's Publication Svcs.

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PRESCRIBING

Importance of pharmacists' order review

With a few exceptions, a pharmacist reviews orders for medications before they are dispensed. After that order is faxed to the pharmacy, what exactly happens before the medication is available for the nurse to administer?

The main purpose of the pharmacist's review is to assure medication safety. Several checks are done.

The pharmacist checks to make sure the patient is not allergic to the medication ordered or a similar drug. Even medications that appear simple, like ibuprofen, can cause devastating effects in a patient with an "aspirin allergy."

The dose, dosage, rate of administration, and route of administration are verified. Pharmacists commonly find 10- to 100-fold overdoses. Medications administered based on mg/kg per unit of time are common problems. A drug intended to be given at a specified mg/kg/hr-dosage can be mistakenly written as mg/kg/min. These 60-fold overdoses are usually just lapses that are easily corrected. Underdosing is an equally important problem.

Pharmacists also check for therapeutic duplication. For example, patients

prescribed a low-molecular weight heparin, like enoxaparin, may inadvertently remain on unfractionated heparin. This duplication would increase the risk of bleeding. One of these medications needs to be stopped.

When you receive a page about a problem order, the pharmacist is trying to avoid a medication error. Please be understanding when a pharmacist contacts you to help you protect your patients.

A similar process identifies other drug interactions. Drug interactions may require a medication to be changed to an alternative, for a dosage to be increased or decreased, or may be acceptable depending on the benefits-to-risk assessment. This will require additional input from the prescriber.

When a problem order is identified, the order is held. The pharmacist then tries to contact the prescriber to get a clarification or change in the order. The prescriber must be paged. A legible signature and the use of a doctor number helps the pharmacist determine who to contact.

It is important that the prescriber answer these pages promptly in order to prevent a long turn-around time for that medication order. Cross-cover may contribute to a long delay. The covering physician is sometimes hesitant to make a change. The resultant delay can result in serious complications. A delay in beginning antibiotics could occur. There have been instances where an important antibiotic has been delayed for more than 8 hours because of difficulty in contacting the prescriber or the covering physician. These errors of omission can be just as serious as other mistakes.

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