Volume 19, Number 8

Shands at the University of Florida

September 2005

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met August 16, 2005. 1 drug was added in the *Formulary* and no drugs were deleted. The criteria for use of 1 drug was modified.

◆ **ADDED**

Trastuzumab
(Herceptin® by Genentech)*

**Restricted to chemotherapy prescribers and administrative approval.*

◆ **DELETED**

None

◆ **CRITERIA FOR USE CHANGED**

Nesiritide
(Natrecor® by Scios)

Trastuzumab is a recombinant humanized monoclonal antibody that selectively binds to the extracellular domain of the HER2 protein. HER2 stands for human epidermal growth factor receptor 2. HER2 is a gene that determines how cells grow, divide, and repair themselves. Cells that are HER2-positive overexpress the HER2 gene and contribute to the rapid cell division of tumor cells. About 25% of breast cancers overexpress the HER2 gene.

The labeled indication for trastuzumab is as a single agent for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received 1 or more chemotherapy regimens for their metastatic disease. It is also has a labeled indication in combination with paclitaxel in patients with breast cancer who overexpress the HER2 protein and who have not received previous therapy for their metastatic disease. Evidence currently supports improved response rates and prolonged disease-free survival with

(continued on next page)

NEWS

P&T Committee action 2004–05

Another year of Pharmacy & Therapeutics (P&T) Committee activity was just completed. The P&T Committee's year goes from July through June. During this time, the Committee met 10 times. The goals of the Committee are to use evidence-based medicine principles to establish drug use policies and to establish a formulary. In addition, medication safety is promoted.

The goals of the Pharmacy & Therapeutics Committee are to use evidence-based medicine principles to establish drug use policies and to establish a formulary. In addition, medication safety is promoted.

The P&T Committee is a medical staff committee that is the formal line of communications between the medical staff and Shands at UF as it relates to all drug-related matters. Currently, 16 medical staff members help decide which drugs are readily available for use, what limitations should be put on those drugs that are available, and what can be done to improve medication safety.

Last year, 37 new products were added in the *Formulary.* Only 9 new drugs were requested, the rest of the additions were proactive actions taken by the P&T Committee. 13 drugs were deleted from the *Formulary.* Drugs listed in the *Formulary* can be found on the Shands intranet at http://intranet.shands.org/pharm/drugs.htm.

25 drugs were reviewed by the P&T Committee and designated nonformulary and not available. These medications cannot be obtained through a nonformulary request.

385 adverse drug reactions were reviewed last fiscal year. Most of the reported reactions were "potentially preventable" and were detected via our tracer drug program. The tracer drug program evaluates patients who receive drugs that may be an indicator of an adverse drug reaction (eg, dextrose 50%, vitamin K, protamine).

Several drug use policies were approved. For example, a policy was approved that allows pharmacists to automatically interchange the individual ingredients for a combination product, when both ingredients are already listed in the *Formulary.* Also, a policy prohibiting presentations of nonformulary drugs by drug manufacturers' sales representatives to hospital employees who cannot request a drug for addition in the *Formulary* was approved. The goal is to decrease nonformulary drug use.

The *Drugs & Therapy Bulletin* remains the primary method for communicating P&T Committee activities throughout the year. Please take the time to read the changes that occur each month. Back issues of the *Bulletin* are available on the Internet at http://www.shands.org/professional/drugs/bulletin.htm

Dr. Gonzalez-Rothi chairs the P&T Committee. This is his 6th year leading this medical staff committee. If you have questions or comments about the activities of the P&T Committee, Dr. Gonzalez-Rothi can be reached by e-mail at RothiRJ@medicine.ufl.edu.

INSIDE THIS ISSUE

Formulary update, *from page 1*
trastuzumab regimens for breast cancer. There are also unpublished data that support the use of trastuzumab as adjuvant therapy in patients who do not have metastatic disease.

Trastuzumab is usually well-tolerated. The most frequent adverse effects are mild to moderate first-infusion reactions typified by fever, chills, and nausea. These reactions occur in as many as 40% of patients, but most patients can be managed with acetaminophen and diphenhydramine. Reactions do not generally reoccur with subsequent infusions. Other adverse effects include asthenia, pain, diarrhea, anemia, and leukopenia.

The 2 most significant possible adverse effects are cardiac toxicity and pulmonary toxicity. Ventricular dysfunction and heart failure are listed as black box warnings for trastuzumab. Left ventricular function should be measured in all patients before and during treatment with trastuzumab. Cardiac dysfunction has been more common in patients when used in combination with anthracyclines and cyclophosphamide.

Generally trastuzumab is given in the outpatient setting. However, there are patients who are too unstable to receive their treatment as outpatients. Trastuzumab was added in the *Formulary* for these patients; however, administrative approval is required.

Loading doses of trastuzumab cost approximately $1500 to $3000, and weekly maintenance doses cost approximately $700 to $2200. These expenses are not considered in inpatient reimbursement schemes.

Nesiritide is a recombinant form of B-type naturetic peptide. Because nesiritide produces venodilation (both arterial and venous) and diuresis, it has a labeled indication for the treatment of acute decompensated fluid-overloaded congestive heart failure. The labeling specifically states that Natrecor® is indicated for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or minimal activity. The dosage is usually administered for 48 hours or less. In the clinical trials used to approve nesiritide, only about 20% of patients received therapy for more than 48 hours.

Nesiritide's pharmacology has led to its use for various off-labeled uses. At Shands at UF, it has been used for its renal-sparing effects in the post-cardiac surgery patient population and as a bridge to transplant in patients with refractory heart failure. There are limited data to support these indications, but the P&T Committee has previously determined that the potential benefits justified these off-labeled uses.

Recently, however, national support for the off-labeled use of nesiritide has waned. After meta-analyses were reported in the literature that associated the use of nesiritide with decreased renal function and increased death rates were published, the manufacturer of nesiritide convened an expert panel to review the use of nesiritide.

This panel recommended that nesiritide use be strictly limited to patients presenting to the hospital with acutely decompensated congestive heart failure who have dyspnea at rest. Further, they listed several indications that nesiritide should not be used based on insufficient evidence, including improving renal function. Adequate clinical trial data do not exist for these off-label uses and the existing clinical trial data are associated with a dose-dependent increase in serum creatinine.

Based on this information, the P&T Committee limited nesiritide use to its labeled indication. Use longer than 48 hours will now require a rewritten order. Nesiritide will no longer be used as a bridge to transplantation or for the prevention of renal dysfunction post cardiothoracic surgery. Use for the prevention of acute renal dysfunction after cardiothoracic surgery will only continue as part of an ongoing investigational protocol.

POLICIES AND PROCEDURES

The Statins: Timing is everything

At the August meeting, the P&T Committee approved a policy that would administer all HMG-CoA reductase inhibitors (eg, atorvastatin, lovastatin, simvastatin) in the evening at 10:00 PM (ie, 2200) to adult patients. With computer-generated medication administration records (MARs), specifying standard dosage times will occur more often…when it makes a clinical difference.

Standardized dosage times already exist for "generic" dosage schedules like "twice a day" (1000 and 2200 for adults or 0800 and 2000 for children) or "at bedtime" (2200 for adults or 2000 for children). There are some medications that are not ordered for a specific time of day, but if given at a specific time, improved efficacy or increased safety can occur. Increased safety may be attributed to decreased likelihood of an adverse reaction or logistical issues that may allow prescribers to react to laboratory monitoring.

For many years, warfarin has been given at 6:00 PM (ie, 1800). Warfarin is not inherently more effective, nor does it cause fewer adverse effects when given at 6:00 PM. However, by delaying the daily dose until the evening, instead of 10:00 AM, which would be typical administration time for most drugs given daily, it provides sufficient time for laboratory results to be reported (ie, INR) and for the prescriber to adjust dosages, when needed. If a morning laboratory draw shows a prolonged INR and a dosage was just given, dosage adjustments are more difficult. Patients also may manifest dose-dependent adverse effects. The evening warfarin dose can increase medication safety by allowing sufficient time for dosages to be adjusted based on laboratory results.

Statins will be given at bedtime (ie, 10:00 PM for adults and 8:00 PM for children) to maximize their effectiveness. The highest amount of cholesterol synthesis occurs at night. Thus, the highest concentration of drugs that inhibit cholesterol synthesis should be present at night.

Hydroxy-methylglutaryl (HMG) Co-A is the substrate used to form mevalonic acid in the liver. It is converted by HMG-CoA reductase to mevalonic acid. Mevalonic acid is then used to form cholesterol. By inhibiting the conversion of HMG-CoA to mevalonic acid, this results in decreased cholesterol in liver cells. This stimulates the uptake of cholesterol from the systemic circulation into liver cells, resulting in decreased serum cholesterol. HMG Co-A reductase inhibitors, or "statins," thus work best when HMG CoA-reductase activity is highest, that is, at night.

The statins with long half-lives (ie, atorvastatin and rosuvastatin) do not have a pronounced difference in effectiveness when given in the morning or the evening. However, giving these agents in the evening will be at least as effective as giving them in the morning. For simplicity, all HMG-CoA reductase inhibitors will be given at the same time.

The P&T Committee endorsed standardized administration times for statins to maximize their effectiveness. When identified, other standardized dosage times will be established to maximize therapy.

Standardized dosage times only apply when an administration time is not specified in the medication order. Physician's orders that contain a specified administration time will be honored.

OUTPATIENT PHARMACY

More information on writing outpatient prescriptions

Correctly writing outpatient prescriptions saves everyone time and helps avoid medication errors. Last year, an article in the November-December issue of the *Bulletin* gave several suggestions for avoiding pages and phone calls to clarify outpatient prescriptions. This article will re-emphasize some of these points and provide some additional suggestions that should be helpful.

State and federal laws mandate that specific elements be included in all prescriptions. A prescription must have the patient's name, drug and strength, quantity, directions for use, number of refills (except for Schedule II controlled substances, which cannot be refilled), prescriber's name, prescriber's address, prescriber's telephone number, and prescriber's DEA number (for controlled substances). Often the number of refills is omitted. If no refills are intended, the prescriber should write "no refills."

Although not mandated by law, it is highly recommended that your patient's weight be provided, especially for pediatric patients. This allows the pharmacist to verify the dosage. Providing the indication for use is also helpful in avoiding medication errors. Writing the patient's medical record number and/or date of birth on the prescription will help the Shands outpatient pharmacists identify the patient in databases that provides additional patient information.

Controlled substances, particularly Schedule II (CIIs) controlled substances (eg, morphine, methylphenidate), have additional requirements. All controlled substance prescriptions require the patient's address in addition to all the other elements required for any prescription. Also, prescriptions of different Schedules may not be written on the same prescription blank. In other words, nonscheduled legend drugs may not be written on the same prescription form with any controlled substance, and CIIs, CIIIs, CIVs, and CVs may not be mixed on the same prescription blank. If you do not know the Schedules of drugs, it is best to write controlled substances on separate prescription blanks.

All prescriptions must be dated. The month must be written out in textural letters. Dates like "9/15/2005" are not acceptable; "September 15, 2005" must be written. Prescriptions cannot be post-dated; each prescription must have the date the prescription is actually written. If you do not want your patients to fill the prescription until a later date, write on the face of the prescription, "Do Not Fill Until <insert date>."

Please remember to state the quantity of drug that should be dispensed with each fill of a prescription. Florida law now requires that prescribers write the quantity of all prescription drugs in numerals and words to prevent adulteration (ie, #10 [ten]). This can help prevent patients from changing the quantity of controlled substance prescribed. Although not required, spelling out the strength in words is also recommended.

Clearly write the name of the drug on each prescription. Be careful when writing for specialized dosage forms, like extended-release products. For example, bupropion (Wellbutrin®) is available as both XL and SR formulations. It is common to receive a prescription written for Wellbutrin XR, which does not exist. This requires a page or telephone call for a clarification.

Finally, always remember to sign your prescription. Signatures are difficult to read, so make sure your name is printed somewhere on the prescription blank. Clarifying a problem prescription is impossible if the prescriber cannot be identified. Problem prescriptions can result in inconveniences for your patients and could result in delays of therapy.

By David Wackerly, PharmD

NEWS

Florida's Medicaid prescription drug list is a big change

Change often makes people uncomfortable: the bigger the change, the greater the discomfort. The changes that took effect July 1, 2005, to the Florida Medicaid drug benefit program have had a major impact on patients (approximately 800,000 statewide), prescribers, and pharmacists.

In the hospital setting, these changes have made the discharge process more difficult. When Medicaid patients are discharged on drugs not now covered by Medicaid, it slows the discharge process. Hopefully, information about the changes in the Medicaid prescription drug program will help minimize potential problems and inconveniences for all those affected. However, the changes will continue to cause delays in pharmacies, slow the discharge process, and create more paperwork and frustrations for prescribers.

In the last legislative session, the Florida Legislature changed the Florida Medicaid prescription drug plan with a goal of cutting $292 million dollars from the estimated $2.5 billion drug budget. To achieve more than an 11% reduction in drug expenditures in the face of increasing drug costs that have averaged greater than 16% per year since 2000 is a lofty goal that requires a major intervention…and the resultant implementation problems.

Previous measures taken by the State to cut Medicaid drug expenditures (eg, 4-brand-name-drug limit, counterfeit-proof prescriptions, quantity limits on prescriptions) have not yielded sufficient reductions. All previous programs to cut Medicaid drug costs have been estimated to save about $500 million dollars. Thus, strict enforcement of the Preferred Drug List (PDL) was chosen to decrease expenditures even further. Prescribing from the PDL is a legislative mandate.

The PDL is a formulary of drugs that can be prescribed for Medicaid patients and are dispensed without any prior authorization. The PDL replaces the old 4-brand-name-drug limit. Now more than 4 brand name drugs can be prescribed for a Medicaid patient, as long as all of the brand name drugs are in the PDL.

The PDL is promoted as a list of drugs that are the least expensive drugs available. Most of the cost savings come from rebates that manufacturers have agreed to give the State of Florida for their products. Rebates are the major source of savings generated by the PDL. It does not, however, always result in the least expensive product being used.

Some generic drugs are not on the list. For example, new prescriptions for generic paroxetine cannot be filled, while brand name Paxil® CR is listed in the PDL. Patients who were on generic paroxetine before July 1, 2005, should have been switched to an alternative by September 11, 2005.

(continued on next page)

Drugs & Therapy
B · U · L · L · E · T · I · N

Volume 19, No. 8 September 2005

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.

EDITOR, DRUGS & THERAPY BULLETIN
Randy C. Hatton, PharmD

DIRECTOR, PHARMACY SERVICES
Alan Knudsen, MS, RPh

CHAIRMAN, PHARMACY & THERAPEUTICS COMMITTEE
Ricardo Gonzalez-Rothi, MD

EDITING, DESIGN, & PRODUCTION
Shands HealthCare's Publication Svcs.

FOR MORE INFORMATION, VISIT US ONLINE
http://shands.org/professional/drugs/bulletin.htm

SHANDS
Shands at the University of Florida
DRUG INFORMATION SERVICE
PO Box 100316
Gainesville, FL 32610-0316

NON-PROFIT ORG.
U.S. POSTAGE
PAID
GAINESVILLE, FL
PERMIT NO. 94

News, *from page 3*

Although the State claims that the prior authorization process is relatively easy, our experience has been that prior authorization is very difficult for drugs not in the PDL. Prescribers must complete a form that justifies a "nonformulary" drug, and these are not often approved. Prior authorization is most often approved when patients have received, but failed all drugs listed on the PDL. There may also be other "clinical" justifications, but these can be problematic. Florida Medicaid requires 24 hours to review the request form for prior authorization. These forms are available on the web at http://www.fdhc.state.fl.us/Medicaid/Prescribed_Drug/pharm_thera/paforms.shtml. A 24-hour delay is problematic at the time of discharge.

While the prior-authorization form is being reviewed, Shands outpatient pharmacists may opt to work with social workers to access hospital funds that have been earmarked to facilitate the discharge process. These funds are limited, however, and clinical justification will be needed. The chances that the prior authorizations will be approved will also be factored in the decision to provide funds. A re-admission because patients do not ultimately receive needed drugs would be a shortsighted use of funds for discharge medications.

There are clinical situations where it does not make sense to start a patient on a non-PDL drug for a few days, and then stop the drug if the prior authorization is not approved (eg, bosentan). Shands Outpatient Pharmacies will work with prescribers on an individual basis to manage these situations.

Some manufacturers have chosen not to participate in the State's rebate program. This has resulted in some high-profile products not being listed in the PDL. For example, when Eli Lilly chose not to pay rebates to the State, a common drug used to treat schizophrenia, olanzapine (Zyprexa®) was not included in the PDL. In the past, mental health drugs were exempt from cost-cutting plans, like the 4-brand-name-drug limit. The new PDL includes (or in this case excludes) mental health drugs. Only drugs used to treat HIV disease, drugs listed in the State's Negative Formulary, and the 72-hour emergency supply of medications are exempt from the PDL list requirements.

The PDL is being implemented in stages, but by October, most initial changes should have gone into effect. The PDL and the proposed implementation dates can be found on the Internet at http://www.fdhc.state.fl.us/Medicaid/Prescribed_Drug/pharm_thera/ccpdl.pdf and the complete PDL list can be found at http://www.fdhc.state.fl.us/Medicaid/Prescribed_Drug/pharm_thera/fmpdl.pdf. Mental health drugs, which will be implemented in September, are the last drugs scheduled to be implemented in this first phase of the PDL.

The PDL will be dynamic. The Florida Medicaid P&T Committee will meet again on September 21, 2005, and more changes to the PDL are anticipated. Agreements may be reached that will avoid major problems when commonly used drugs are excluded from the PDL. For example, the most commonly dispensed brand name drug, Lipitor® (atorvastatin) is not currently listed in the PDL and will not be available to Florida Medicaid patients after September 30, 2005 unless a rebate agreement is reached with Pfizer.

Please refer to the PDL website for changing information on the State of Florida's Medicaid prescription drug benefit plan. In addition, prescribers can call the Outpatient Pharmacy at 265-8270 and ask for a Pharmacy Coordinator or the Assistant Director for Ambulatory Services to get additional information on the PDL for your Medicaid patients. This is particularly important before you plan to discharge your patients from the hospital.