

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met April 17, 2007. No drugs were added in the *Formulary*, and 1 drug was deleted. 3 drugs were designated nonformulary and not available. The criteria-for-use were changed for 5 drugs.

◆ ADDED

None

◆ DELETED

Tegaserod
(Zelnorm® by Novartis)*

*Nonformulary and not available

◆ NONFORMULARY AND NOT AVAILABLE

Lidocaine transdermal patches
(Lidoderm® by Endo)

Pergolide (Permax® and generics)

◆ CRITERIA-FOR-USE CHANGES

Albumin (Generic)[†]

[†]When supplies fall, restricted to approval by a Clinical Pharmacist

Ceftriaxone (Generic)[‡]

[‡]May be streamlined or discontinued by the Antibiotic Management Program

Darbepoetin
(Aranesp® by Amgen)[§]

Epoetin
(Procrit® by Ortho Biotech)[§]

[§]Automatically discontinued if a patient's hemoglobin is >12 g/dL

Lansoprazole intravenous
(Prevacid® IV by TAP)**

**Restricted to nonvariceal upper GI bleeding and strict NPO

Tegaserod is a selective partial agonist at the receptor subtype 4 of serotonin (5-HT₄). It has been used for constipation-predominant irritable bowel syndrome (IBS) and chronic constipation.

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OUTPATIENT PHARMACY

Charity Care Formulary additions

New drugs were added in the *Charity Care Formulary* to offer options for the treatment of diabetes and hyperlipidemia. The brand of 1 device was changed.

Extended-release glipizide, extended-release metformin, TrueTrack® glucometers and test strips, and pravastatin are now available as inexpensive alternatives to brand name products in the *Charity Care Formulary*. These additions are consistent with the move away from brand name products and towards generic drugs, which now cover a wide array of therapeutic options for most conditions.

Manufacturer support for the *Charity Care Formulary* has been inconsistent. The costs associated with keeping products in the *Charity Care Formulary* after manufacturers stop their support often negate the savings even when provided at hospital cost. Thus, whenever possible, inexpensive generic products will be used in lieu of brand name products.

Extended-release glipizide tablets are a generic version of Glucotrol® XL, a oral sulfonylurea used for many years for the management of type 2 diabetes mellitus. Extended-release metformin tablets are a generic version of Gluco-

phage® XR, an oral biguanide hypoglycemic agent also used to treat type 2 diabetes mellitus. Metformin ER has also been used off-label to treat infertility and polycystic ovary syndrome.

The TrueTrack® Smart System glucometer now replaces the OneTouch® glucometer in the *Charity Care Formulary*. TrueTrack® test strips also replace the OneTouch® test strips. Glucometers are inexpensive, but the test strips can be very expensive. The TrueTrack® test strips cost a third of the cost of the OneTouch® strips. OneTouch® glucometers and strips are still available in the Outpatient Pharmacy for funded prescriptions (eg, State of Florida or Medicaid).

Pravastatin offers a HMG-CoA reductase inhibitor that has a low incidence of drug interactions. It can be used with transplant drugs or drugs used to treat patients infected with HIV. Pravastatin is a generic version of Pravachol®, which has been used successfully for many years to lower LDL cholesterol and improve patient's cardiovascular outcomes.

The complete list of therapeutic options in the *Charity Care Formulary* can be found on the intranet at <http://intranet.shands.org/pharm/ccform.htm>.

Generics keep patients out of the "donut" hole

Recently released data from a large pharmacy benefit manager (ie, Express Scripts) shows that generics keep elderly patients out of the "donut hole" in their Medicare Part D prescription benefit plans. Medicare Part D plans provide a prescription benefit plan for patients eligible for Medicare and Social Security Disability. These plans work like any prescription benefit plan, which require patients to pay copays for their prescriptions. Patients are given financial incentives to use less

expensive generics. Copays for each prescription are considerably less when generics are prescribed.

However, additional substantial cost savings in Medicare Part D plans come

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◆ INSIDE THIS ISSUE

◆ IVs standardized

Formulary update, from page 1

On March 30, 2007 the Food and Drug Administration (FDA) requested that Novartis Pharmaceuticals Corporation voluntarily stop marketing Zelnorm® based on recent findings of increased risk of serious cardiovascular adverse events associated with its use. Novartis agreed to voluntarily suspend marketing of the drug in the United States.

Zelnorm® was originally approved by FDA in July 2002 for the labeled indication of short-term treatment of women with irritable bowel syndrome whose primary symptom is constipation. It was added in the *Formulary* in November 2003. Zelnorm®'s labeling was changed in August 2004 to add the treatment of chronic constipation for men and women under age 65 as an indication.

The FDA is currently advising patients who are using Zelnorm® to contact their health care providers to discuss treatment alternatives. Patients who are taking Zelnorm® are being advised to seek emergency medical care if they experience severe chest pain, shortness of breath, dizziness, sudden onset of weakness or difficulty walking or talking, or other symptoms of a heart attack or stroke.

Novartis recently reported the results of a new analysis of 29 short-term (1–3 months) randomized, controlled clinical trials of Zelnorm®. The FDA concluded that, based on these data, for most patients the benefits of this drug no longer outweigh its risks.

The analysis included more than 11,600 patients treated with Zelnorm® and over 7000 patients treated with placebo. The data showed that the risk of serious cardiovascular adverse events (eg, angina, heart attacks, and strokes) associated with use of Zelnorm® is higher than with placebo treatment. 13 Zelnorm®-treated patients (or 0.1%) had confirmed cardiovascular ischemic events, and only 1 placebo-treated patient (or 0.01%) had an event (ie, a greater than 10-fold increase in risk).

The FDA is working with Novartis to allow access to Zelnorm® as an investigational drug for patients with no other treatment options when the benefits may outweigh the risks. The FDA has also indicated to Novartis the possibility of considering limited re-introduction of Zelnorm® at a later date, if a population of patients can be identified in which the benefits of the drug outweigh the risks.

Lidoderm® patches were evaluated by the P&T Committee and designated nonformulary and not available. Lidoderm® transdermal patches

deliver a small amount of lidocaine local anesthetic from the adhesive in the patches. The amount of lidocaine delivered is low enough that sensory block is not achieved; however, a local analgesic effect under the area covered by the patch can occur for neuropathic pain conditions.

Lidoderm® patches have a labeled indication for the relief of pain associated with post-herpetic neuralgia. At Shands at UF, these patches have been used extensively off-label for rib and sternum fracture pain.

Clinical trials show modest effectiveness for Lidoderm® for the treatment of post-herpetic neuralgias, and there are several equally effective or superior treatment options available in the *Formulary* (eg, amitriptyline, gabapentin). There are no published data supporting the use of Lidoderm® patches for the treatment of rib and sternum fractures. There is an ongoing study at Shands at UF that may help provide some insight in the usefulness of Lidoderm® for this off-labeled use. Unfortunately, the manufacturer would not provide or sell placebo patches to help facilitate the study of Lidoderm® for this off-labeled use.

Pergolide is a semi-synthetic ergot alkaloid and dopamine agonist. It has been on the market since 1988 with a labeled indication for the treatment of Parkinson's disease in combination with levodopa. It has never been listed in the *Formulary*, has rarely been requested for nonformulary use, and in the last year, it has not been used at all. In 2006, only an estimated 12,000 patients received prescriptions for pergolide from retail pharmacies in the United States.

On March 29, 2007, the FDA announced that manufacturers of pergolide products will voluntarily remove these drugs from the market because of the risk of serious damage to patients' heart valves. The FDA is advising that patients taking pergolide should contact their physicians to discuss alternate treatments and that patients should not stop taking the medication, as stopping pergolide abruptly can be dangerous (ie, precipitating central nervous adverse effects including confusion and hallucinations).

There are alternative therapies available for Parkinson's disease, including other non-ergotamine dopamine agonists, which have not been associated with valvular heart disease (eg, pramipexole). The removal of pergolide products is not expected to adversely affect patient care because of its low use and because of the availability of alternative therapies. Patients will need to be titrated off their pergolide while titrating up their new alternative therapy.

Recent studies published in the *New England Journal of Medicine* confirm previous findings associating pergolide with increased risk of regurgitation of the mitral, tricuspid, and aortic valves of the heart. In light of this additional post-market safety information, the companies that market pergolide will stop shipping pergolide for distribution and, in cooperation with FDA, will withdraw the products from the market.

Valvular heart disease was first described in association with pergolide in 2002. In 2003, valvulopathy was added to the warnings section of Permax®'s labeling, at which time a *Dear Healthcare Practitioner* letter was sent by Lilly. In 2006, the warning was upgraded to a black box warning because of new data concerning risks of heart valve damage.

The effect of the voluntary withdrawal on supplies of pergolide currently in pharmacies will not be immediate. This delay will allow time for health care providers and patients to discuss appropriate treatment options and to have time to change treatments.

Albumin has been in short supply for the last several months. Insufficient collections and/or processing of human plasma have been blamed for this ongoing shortage. The shortage continues to be a problem and in recent months, despite attempts to encourage more limited use, we have come very close to exhausting our albumin supplies. Once we use our entire monthly allotment of albumin, there is no source to acquire additional product.

The supply of albumin on hand at Shands at UF is continually monitored, and pharmacists have been working with major prescribers to voluntarily restrict their use of albumin in order to assure a supply of product for the neediest patients at the end of each month. Shands receives an allocation of albumin shortly after the beginning of each month. With current usage, there is little product left at the end of each month. Therefore, the P&T Committee approved a restriction process that allows the prioritization of use by indication when supplies are projected to be exhausted.

Criteria were established by identifying circumstances when patients would be harmed by not using albumin. For example, an allotment of albumin will be held in reserve for processing stem cells for transplantation because without albumin this service cannot function.

Criteria for use were grouped into 4 categories. These categories include
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Formulary update, from page 2 approved uses (for pediatrics and adults), approved pediatric (specific) uses, approved uses based on serum albumin levels, and an emergent shortage restriction list that includes indications that will not be allowed when supplies are low. Approved uses include thermal injury/burn patients, large volume (greater than 5 liters) paracentesis for cirrhotic patients, ECMO circuit priming, and the stem cell laboratory for preparation of stem cell transplants. Specific approved uses in pediatric patients include volume expansion in neonates after crystalloid (used first) failed, hyperbilirubinemia of the newborn if phototherapy failed, and pediatric cardiac surgery patients. Approved uses based on serum albumin levels include hepatic resection and liver transplant with an albumin less than 2.5 g/dL, and for volume resuscitation with an albumin less than 2 g/dL. The restricted indication list includes hypotension during dialysis, decreased cerebral perfusion pressure, cardiac surgery, and nutritional intervention.

When the supply of albumin is projected to be exhausted (eg, 25% of the monthly supply remaining with more than 1 week left in the month), a clinical pharmacist will have to approve each use based on the P&T Committee-approved criteria for use. These pharmacists will be supported by back-up faculty physicians.

Ceftriaxone is an injectable third-generation cephalosporin with a broad spectrum of activity that includes both gram-positive (eg, *Streptococcus*) and gram-negative (*Enterobacteriaceae*) organisms. Ceftriaxone has proven efficacy in the treatment of many infections, including urinary tract infections (UTIs), pulmonary infections (eg, Community Acquire Pneumonia [CAP]), central nervous system infections (eg, meningitis), and intra-abdominal infections. It is recommended in guidelines for empiric therapy for CAP in patients requiring hospitalization and for patients with suspected community-acquired meningitis.

While the utility of ceftriaxone has been documented, its use has been associated with undesirable effects. Increased ceftriaxone consumption has been correlated with an increased incidence of *Clostridium difficile*-associated diarrhea. The high concentrations of ceftriaxone in the bile and alteration of gastrointestinal bacterial flora may contribute to this complication. Ceftriaxone is also associated with the selection of bacteria that may produce potent beta-lactamases in some gram-negative pathogens known as chromosomal AmpC cepha-

losporinase. Organisms capable of producing AmpC cephalosporinase are resistant to all commercially available beta-lactam antibiotics. Thus, prudent use of ceftriaxone will help maintain current bacterial susceptibilities and decrease the risk of *Clostridium difficile*-associated diarrhea.

The P&T Committee approved the following criteria for ceftriaxone use: empiric treatment of CAP; empiric treatment of COPD exacerbations; empiric treatment of suspected meningitis, and for definitive therapy for documented *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus agalactiae*, *Escherichia coli*, and other Enterobacteriaceae CNS infections resistant to narrower spectrum agents; for the empiric treatment of complicated UTIs pending culture and sensitivities; for the treatment of spontaneous bacterial peritonitis; and, definitive therapy for documented pathogens resistant to other narrower-spectrum agents.

The Antibiotic Management Program (AMP) is now authorized to streamline or discontinue ceftriaxone therapy once culture results are known and/or infection is ruled out. Streamlining will be based on culture and sensitivity results. The AMP is also authorized to discontinue therapy once the patient has completed an appropriate treatment course. The primary and consulting services will be notified before the ceftriaxone order is changed or discontinued.

Darbepoetin and epoetin are erythropoietins or Erythropoiesis-Stimulating Agents (ESAs). These ESAs all act in the same way and have the same safety concerns.

Recently, the FDA issued a Public Health Advisory for ESAs. This report states that ESAs have been associated with a increased rate of tumor growth in patients with head and neck cancer and breast cancer, a higher death rate and no fewer blood transfusions in patients with cancer and anemia not receiving chemotherapy, a higher death rate and thrombotic complications (eg, blood clots, strokes heart attacks) in patients with chronic kidney failure with hemoglobins greater than 12 g/dL, and more thrombotic complications in patients scheduled for major surgery compared with usual blood conservation care.

Based on these safety concerns, the P&T Committee approved a policy that changes the standard administration time for darbepoetin and epoetin to 1800 and requires that any of these drug regimens be stopped when a hemoglobin value above 12 g/dL has been measured.

Lansoprazole IV is the injectable proton-pump inhibitor (PPI) listed in

the *Formulary*. The manufacturer of lansoprazole IV recently announced that this drug has been discontinued; however, we still have several months' supply before the injectable PPI in the *Formulary* will need to be changed. This supply may last longer than expected now that the P&T Committee has restricted the use of IV PPIs to only patients with a non-variceal upper gastrointestinal (GI) bleed or in patients who are strictly NPO (ie, unable to take a PPI suspension down a tube or the orally dissolvable tablets [ODT] by mouth).

In order to use an IV PPI, each order must be approved by a clinical pharmacist who will verify that the use meets the above criteria. Orders will be approved between 7 am and 11 pm similar to restricted anti-infective agents. Orders written from 11 pm to 7 am will be started, but will be discontinued if the approved criteria are not met.

It is anticipated that most of the use of IV PPIs will now be constant infusions for the prevention of rebleeding after therapeutic endoscopies. Intermittent doses of IV PPIs should be extremely rare, which should help avoid the problems with product shortages that have plagued this category of drugs. The supply of IV PPIs will now be allocated to the neediest patients. All pre-printed orders for IV PPIs will be changed to match the changes in the approved criteria for use.

Outpatient pharmacy, from page 1 from keeping patients out of the donut hole when they are responsible for the entire cost of their prescriptions. In 2007, once patients reach the \$2400 limit for Medicare Part D programs, they must meet a \$3850 out-of-pocket maximum before benefits once again kick in. The time from the \$2400 initial benefit limit to the \$3850 out-of-pocket maximum is commonly referred to as "the donut hole."

Medicare Part D has been a fairly successful program, and polls show that most seniors appreciate the benefit. Before Medicare Part D, many patients were essentially "in the hole" all the time because they had to pay the total costs for all of their prescriptions. Seniors quickly adjusted to the lower costs associated with their copays and are often shocked when they have to go back to paying full price.

The Express Scripts study of 220,000 seniors with higher incomes (ie, not Medicare Part D beneficiaries eligible for reduced rates because of low incomes) found that 23% of the patients who entered the donut hole

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Volume 21, No. 5

May 2007

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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Shands HealthCare's Publication Svcs.

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POLICIES AND PROCEDURES

Standardized IV concentrations

In September 2006, standard concentrations for intravenous products were established for pediatric patients. Standard concentrations have now been established for adults in order to comply with Joint Commission-mandated medication safety standards. By policy, these standard concentrations must be used for the drugs listed.

The adult and pediatric lists contain several options that allow flexibility in providing dilute concentrations that allow the titration of low dosages and concentrated solutions for patients who are fluid-restricted. By establishing standard concentrations, errors

that have been associated with having an unlimited number of options for the concentrations of IV drugs can be prevented.

The Joint Commission established National Patient Safety Goals in order to improve the safety and quality of care and avoid risks to patients. The Joint Commission has a relatively short list of issues that they emphasize each year when they survey and accredit hospitals. Standard 3b states that hospitals will "standardize and limit the number of drug concentrations used by the organization." Since oral medica-

tions already come in a limited number of concentrations, the emphasis of this standard has been given to parenteral medications.

High-alert medications, which include but are not limited to electrolytes, intravenous anticoagulants, insulins, opioids, cardioactive drugs, vasopressors, and antihypertensives, are emphasized; however, the principle of standardization is applied to all drugs, which improves the safety of care for patients. Therefore, broad implementation of this Joint Commission mandate has been approved by the P&T Committee.

Outpatient pharmacy, from page 3 could have avoided this fate if they had used generic alternatives. Of all patients in this study, 22% hit the donut hole and more than half did so by August. Generic use in the group that entered the donut hole was lower than those who did not (ie, 53% versus 67%).

Patients who rely on Medicare Part D for their prescriptions benefit from greater use of generics. Generics lower their copays and prevent them from reaching the limit that requires them to pay for the entire cost of their prescriptions. As more and more drugs become available as generics, there are often good alternatives in a therapeutic class that lower patients' costs (eg, generic

simvastatin as a statin instead of Lipitor®).

Pharmacists in the Outpatient Pharmacy can recommend alternatives that are available as generics. Questions about Medicare Part D can be directed to HARBIJW@shands.ufl.edu, or upon request, a pharmacy representative can provide a Medicare Part D inservice for your division.