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B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met April 15, 2008. 5 drugs were added in the *Formulary,* and 2 drugs were deleted. 12 products were designated nonformulary and not available; 1 criteria for use was changed; and 1 interchange was approved.

◆ ADDED

Alendronate (Generic by Teva)*

**Restricted to pharmacist approval in patients hospitalized ≥ 7 days*

Caspofungin
(Cancidas® by Merck)†

†Restricted to Peds ID or Clinical Pharmacist approval for children < 2 yrs old.

Cefotetan (Generic by APP)

Diphtheria-Tetanus-Acellular Pertussis
(Tripedia® by Sanofi Pasteur)

Modafinil (Provigil® by Cephalon)

◆ DELETED

Cefoxitin (Generic)‡

‡Nonformulary and not available & interchanged to cefotetan

Edrophonium (Enlon® by Baxter)§

§No longer marketed; nonformulary and not available after supplies are exhausted

◆ NONFORMULARY AND NOT AVAILABLE

Alendronate with Vitamin D
(Fosamax® Plus D by Merck)¶

¶Patients cannot use their home meds

Armodafinil
(Nuvigil® by Cephalon)**

***Not currently being marketed*

Edrophonium + Atropine
(Enlon® Plus by Baxter)§

§No longer marketed

(continued on next page)

NEWS

Controversy over requirements for verbal CIII prescriptions

On June 15, 2007, Florida Governor Crist signed HB 1155 amending existing law on the dispensing of controlled substances by a pharmacist.[1] The law officially took effect on July 1, 2007.

The changes in the law are intended to help limit controlled substance diversion. One notable change involved verbal (eg, telephoned) Schedule III (CIII) prescriptions. This new legal requirement can be found in the Florida Statutes Title XLVI Chapter 893.04(2)(e), which states, "A pharmacist may not dispense more than a 30-day supply of a controlled substance listed in Schedule III upon an oral prescription issued in this state."[2]

Based on questions received in the Drug Information and Pharmacy Resource Center, there appears to be controversy over the interpretation of this statute. Some pharmacists believe that the statute limits verbal CIII prescriptions to a single 30-day fill with no refills. Others believe that the phoned-in prescriptions can have up to the maximum legal limit of refills for Schedule III drugs (ie, 5 refills in 6 months) as long as each fill is restricted to a 30-day supply. At this time, it is unclear which interpretation is correct.

When the Florida Board of Pharmacy was contacted for clarification of this issue, they did not have an official interpretation of the new statute. A formal request for clarification to the Board has been sent, but at this time interpretation of the law is left up to the professional judgment of individual pharmacists. Since the law's intent is to prevent diversion, the more conservative interpretation (ie, no refills) will be used by some community pharmacists.

By Russell McKelvey, PharmD

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1. Florida House of Representatives: HB 1155 - Controlled Substances. Available at: http://www.myfloridahouse.gov/sections/Bills/billsdetail.aspx?BillId=36177. Accessed: 4/24/08.
2. Online Sunshine. The 2007 Florida Statutes Title XLVI 893.04 - Pharmacist and practitioner. Available at: http://www.leg.state.fl.us/Statutes/index.cfm?App_mode=Display_Statute&Search_String=&URL=Ch0893/Sec04.HTM. Accessed: 4/24/08.

Free samples aren't free...

Of the estimated $57.5 billion spent on drug promotion in the US in 2004, roughly 30% has been attributed to samples.[1] This is only second to detailing, which comprises 36% of all promotional spending. Pharmaceutical companies expect to get a return on this investment.

Samples do influence prescribing behavior.[2] When samples run out, a prescription is usually written for the sampled drug. In a study published in April, patients receiving samples spent $166 on prescriptions in the 6 months before they obtained free medicine, $244 when they received the samples, and $212 in the 6 months after that.[3] Patients who never received free samples spent an average of $178 in 6 months. For most patients, samples do not lower drug costs.

Most samples are used for patients with insurance, but sometimes samples are given to patients who cannot pay for medications. Samples have never been intended to permanently treat patients. Patient-assistance programs that help low-income patients who are not insured or who are under-insured can be found at www.needymeds.org. This is an alternative to the use of samples for patients who have difficulties paying for their prescriptions.

Samples are a form of drug promotion that may end up costing patients more than lower-cost alternatives like patient-assistance programs or generic alternatives to brand name drugs.

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1. Gagnon MA, Lexchin J. The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States. PLOS Medicine 2008;5:e1-
2. Adair RF, Holmgren LR. Do drug samples influence resident prescribing behavior? A randomized trial. Am J Med. 2005;118:881-4.
3. Alexander CG, Zhang J, Basu A. Characteristics of patients receiving pharmaceutical samples and association between sample receipt and out-of-pocket prescription costs. Med Care 2008;46:394-402.

Formulary update, *from page 1*

◆ NONFORMULARY AND NOT AVAILABLE (cont.)

Etidronate (Generic)

Heparin 10,000-Unit/mL Vials (Generic)††

††After current supplies have been exhausted

Ibandronate Injection & Tablets§ (Boniva® by Roche)‡‡

‡‡Patients cannot use their home meds

Risedronate (Actonel® by Proctor & Gamble)‡‡

‡‡Patients cannot use their home meds

Risedronate with Calcium (Actonel® with Calcium by Proctor & Gamble)‡‡

‡‡Patients cannot use their home meds

Tiludronate (Skelid® by Sanofi-Synthelabo)

Zoledronic Acid Injection 5 mg (Reclast® by Novartis)

◆ THERAPEUTIC INTERCHANGES

Cefotetan for Cefoxitin‡

‡mg-for-mg for surgical prophylaxis

◆ CRITERIA FOR USE CHANGES

Coagulation Factor VIIa, Recombinant (NovoSeven® by Novo Nordisk)§§

§§Automatic dose rounding

Alendronate is an oral bisphosphonate used primarily for the treatment of osteoporosis (eg, from estrogen deficiency, aging, or corticosteroids). Bisphosphonates have also been used for the treatment of hypercalcemia of malignancy and Paget's disease. Bisphosphonates work by inhibiting osteoclast activity and preventing bone resorption.

A bisphosphonate category review resulted in the addition of alendronate in the *Formulary.* Alendronate is now restricted to use in patients who have been hospitalized for at least 7 days and who can take it according to the labeled directions for use. Patients hospitalized less than 7 days will not be harmed by a delay in therapy.

The order for alendronate must specify that it be taken with a full glass of plain water first thing upon arising for the day and at least 30 minutes before the first food, beverage, or medication of the day. Taking alendronate tablets with plain water and avoiding foods and beverages for at least 30 minutes prevents interactions that would prevent or minimize the absorption of alendronate. Less than 1% of a dose of alendronate is normally absorbed, and interactions that would decrease absorption would decrease or eliminate its effectiveness. To reduce the potential for esophageal irritation, patients must not lie down for at least 30 minutes and until after their first food of the day.

Alendronate is the only oral bisphosphonate allowed at Shands at UF. All other oral bisphosphonates (ie, **Fosamax® Plus D**, **etidronate**, **ibandronate**, **risedronate**, **Actonel® with Calcium**, and **tiludronate**) are nonformulary and not available. Patients may not use their own supply from home. If a patient needs an oral bisphosphonate and they can take it safely, alendronate is their only option. A pharmacist will have to approve the use of alendronate before it will be dispensed. They will evaluate whether the order for alendronate is sufficient to decrease the risk of esophageal irritation.

Oral bisphosphonate use has been associated with esophagitis, but also esophageal ulceration, perforation, and strictures. The risk of these adverse effects is minimized by the correct administration technique. The restrictions on alendronate (and the designation of all other oral bisphosphonates as nonformulary and not available) is to provide an option for long-term patients but to minimize the risk of adverse effects.

The bisphosphonate review also included injectable products. Zoledronic acid (Zometa®) was added in the *Formulary* in January 2002 for use in the Outpatient Bone Marrow Transplant Clinic. Pamidronate remains in the *Formulary* and is the injectable bisphosphonate of choice. The main advantage of zoledronic acid is a shorter infusion time compared with pamidronate. The 15- to 30-minute infusion time is an advantage compared with the 2 to 4 hours needed for a pamidronate infusion. In the clinic setting (ie, Outpatient Bone Marrow Transplant Clinic), the shorter infusion time could increase patient turnover. Because pamidronate injection is generic, it is less expensive than zoledronic acid and the difference in cost should be considered.

Ibandronate injection, which is designed for every 3-month administration, and **zoledronic acid 5-mg injection** (**Reclast®**), which is designed for once-a-year administration, should not be used in the hospital for financial reasons. Reimbursement in the inpatient setting does not cover their costs. In the outpatient setting, reimbursements do cover the costs of these drugs.

Caspofungin is an echinocandin antifungal added in the *Formulary* for use in children less than 2 years of age with invasive fungal infections. It is restricted to approval by Pediatric Infectious Diseases or a clinical pharmacist. This offers an alternative to anidulafungin (Eraxis®), which has not been studied in this population. Anidulafungin remains the primary echinocandin listed in the *Formulary.* The echinocandins are considered equivalent and interchangeable, but anidulafungin is the representative of this class listed in the *Formulary* because it currently is the least expensive option.

Cefotetan is a cephamycin antibiotic that was originally added in the *Formulary* in February 1988 due to an improved pharmacokinetic profile versus cefoxitin. Unfortunately, in late 2004 production ceased, and it was removed from the *Formulary.* **Cefoxitin** was added in the *Formulary* as a replacement. Since that time, all orders for cefotetan have been changed to cefoxitin via a P&T-approved interchange. In August 2007, APP received approval for generic cefotetan injection and product is available.

Cefotetan and cefoxitin are both primarily used for pre- and peri-operative antibiotic prophylaxis for certain abdominal, colorectal, obstetric-gynecologic, and urologic surgeries and are identical in terms of their spectrum of pathogen coverage. Cefotetan's prolonged half-life enables less frequent intraoperative (every 8 hours versus every 4 hours with cefoxitin) and less frequent postoperative dosing (every 12 hours versus every 4 to 6 hours with cefoxitin). In addition, it is slightly less expensive than cefoxitin.

Cefotetan is again the preferred cephamycin in the *Formulary* and cefoxitin is nonformulary and not available. In addition, an interchange was approved using the following criteria. For surgical prophylaxis, cefotetan will be given for cefoxitin on a milligram-for-milligram basis. However, because cefoxitin has a shorter half-life than cefotetan, cefotetan will be given less frequently than cefoxitin for moderate and severe infections. For moderate to severe infections when cefoxitin 2 grams IV every 6 hours is prescribed, cefotetan 2 grams IV every 12 hours will be substituted. For severe infections when cefoxitin 2 grams IV every 4 hours is prescribed, cefotetan 3 grams IV every 12 hours will be substituted. Pharmacists will call to change to cefotetan when the cefoxitin order does not meet these criteria.

Tripedia® is a trivalent pediatric vaccine containing **diphtheria, tetanus, and acellular pertussis** or **DTaP**. It was considered for formulary addition because it is a frequently ordered nonformulary drug. Its addition in the *Formulary* and appropriate

(continued on next page)

Formulary update, *from page 2*
listing compared with adult tetanus-diphtheria-acellular pertussis vaccine (Tdap) should decrease confusion with these products and decrease the risk of medication errors.

There are several brands of DTaP products (eg, Daptacel®, Infanrix®, and Tripedia®) that are considered equivalent, despite some differences in the contents and methods of standardization. Daptacel® and Adacel® (ie, the Tdap product listed in the *Formulary*) are look-alike and sound-alike products, which could lead to confusion (between DTaP and Tdap); thus, Tripedia® offers an advantage over Daptacel®.

The Advisory Committee on Immunization Practices (ACIP) considers the available data on the safety and efficacy of these products to be insufficient to express a preference between the available DTaP products available in the US. Any DTaP product may be used to complete the vaccination series. Although ACIP states that it would be optimum to stay with the same brand, this information is often not known.

DTaP is used for the activation of active immunity against diphtheria, tetanus, and pertussis in infants and children from 6 weeks up to 7 years of age. ACIP recommended that pediatric DTaP be used routinely as a 5-dose DTaP schedule at ages 2, 4, 6, 15 to 18 months and 4 to 6 years. Interrupting the recommended schedule or delaying doses does not require the series to be restarted. Tetanus-diphtheria toxoid (Td) or Tdap is used for patients after 7 years of age. A delay in the series delays adequate protection, but does not affect ultimate efficacy.

Children who have had a documented pertussis infection must receive pediatric diphtheria-tetanus toxoid without pertussis (DT) instead of DTaP (ie, DTaP is contraindicated in these patients). Children should not receive DTaP if they have a febrile illness or an acute infection; however, a minor upper respiratory infection is not usually a reason to defer immunization.

Like all childhood vaccines, the following must be documented in the patient's medical record according to federal law: the manufacturer and lot number; the date of administration; and, the name, address, and title of the person administering the vaccine.

Modafinil was reviewed for possible addition in the *Formulary* due to relatively high nonformulary use and because it is a Schedule IV controlled substance. Nonformulary controlled substances are problematic. Patients cannot use their supply from home, and obtaining these products is logistically difficult.

Modafinil is a unique wakefulness-promoting agent with FDA labeled indications for narcolepsy, obstructive sleep apnea, and shift-work disorder. Modafinil has many off-label uses, including ADHD, fatigue due to Parkinson's disease, fatigue due to multiple sclerosis, recovery from general anesthesia, cocaine and amphetamine dependence, atypical and bipolar depression, and schizophrenia.

The exact mechanism of action of modafinil is not fully understood; however, limited animal studies demonstrate that modafinil may increase excitatory glutaminergic transmission in the thalamus and hippocampus. Modafinil is a racemic compound of R- and S-modafanil. The enantiomers have different pharmacokinetics; the half-life of the R-enantiomer is 15 hours and is 3 times longer than the S-enantiomer. The major route of elimination is via liver metabolism (including CYP3A4) and dosages should be reduced by 50% in patients with moderate to severe hepatic impairment.

There are no head-to-head trials comparing modafinil with other stimulant medications. There have been several large phase III clinical trials that have established the safety and efficacy of modafinil for the treatment of its labeled indications and ADHD. Modafinil may be promising in certain off-label uses, such as cocaine dependence and recovery from anesthesia, but more research is needed. Results have been mixed in other off-label uses. Discontinuation of modafinil has not been associated with withdrawal or major rebound symptoms.

Adverse effects associated with modafinil are generally mild and include headache, nervousness, anxiety, and insomnia; however, there have been postmarketing reports of severe rashes, including Stevens-Johnson syndrome, and psychiatric disturbances. Modafinil also has the potential to interact with drugs affecting the CYP3A4, 2C9, and 2C19 enzyme systems.

Modafinil was added in the *Formulary* for continuity of care in patients hospitalized on modafinil.

Armodafinil, the R-isomer of modafinil, was recently approved by the FDA but reportedly will not be marketed until 2010. It was designated nonformulary and not available.

Edrophonium is a cholinesterase inhibitor that competitively inhibits the hydrolysis of acetylcholine. It has labeled indications for the differential diagnosis of myasthenia gravis and as an adjunct in the evaluation of treatment requirements in this disease. It was also used for evaluating emergency treatment in myasthenic crises. Because of its brief duration of action, it was not recommended for maintenance therapy in myasthenia gravis. Edrophonium was also used when a curare antagonist was needed to reverse the neuromuscular block (ie, a block produced by tubocurarine). It is not effective against a succinylcholine chloride neuromuscular block. Although edrophonium could be used adjunctively in the treatment of respiratory depression caused by tubocurarine overdosage, tubocurarine was deleted from the *Formulary* in October 2002 when it was removed from the market. **Enlon-Plus®** (a combination of edrophonium plus atropine) only had a labeled indication as a reversal agent or antagonist of nondepolarizing neuromuscular blocking agents (ie, tubocurarine) and was not used at Shands at UF.

The edrophonium test (or "Tensilon® test" [note the name of this test is based on an older brand name for edrophonium]) rapidly reverses muscle weakness in patients suspected of having myasthenia gravis. There is no pharmacologic alternative to edrophonium for this indication, but there are other nonpharmacologic diagnostic tests that can be used. Baxter Healthcare Corporation announced that it discontinued the distribution of Enlon® and Enlon-Plus®. Reportedly Baxter had problems getting edrophonium from their supplier (Akorn), who had quality control issues. There is no alternate supplier of edrophonium. Once our limited supplies are exhausted, edrophonium will no longer be available.

Concentrated **heparin 10,000 units per milliliter** was deleted from the *Formulary* and designated nonformulary and not available to improve patient safety. Heparin is an anticoagulant used for various prophylactic and therapeutic purposes.

Serious errors reported nationally with concentrated heparin usually occur with the 10,000 unit/mL strength; therefore, it was determined that the best way to minimize risk is to eliminate this strength of heparin (ie, make 10,000-unit/mL heparin nonformulary and not available). The 10,000 unit/mL strength is often confused with less concentrated heparins (eg, 100 unit/mL).

The most concentrated heparin listed in the *Formulary* is now 5000 units per mL. Most areas will use pre-made heparin in dextrose 5% bags. The small amount of dextrose in the pre-made heparin bags is not a problem for patients with diabetes.

Coagulation factor VIIa is a recombinant product similar to human plasma derived factor VII. Factor VII

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Formulary update, *from page 3*
initiates the coagulation cascade, which results in the conversion of prothrombin to thrombin and, ultimately, the formation of a fibrin and a hemostatic plug. NovoSeven® has labeled indications for treatment of bleeding and prevention of bleeding in patients with factor VII deficiency (replacement therapy) and for pharmacologic prevention and treatment in patients with hemophilia A (factor VIII deficiency) or hemophilia B (factor IX deficiency) when patients have inhibitors to factors VIII and IX. NovoSeven® also has a labeled indication for the prevention of surgical bleeding in patients with hemophilia and factor inhibitors.

Factor VIIa has also been used for multiple off-label uses (eg, post CT surgery bleeding [in patients without hemophilia], trauma). Unfortunately, inpatient reimbursements do not cover off-label uses. Also, thrombosis is a concern.

NovoSeven® is extremely expensive and multiple proposals are being considered to decrease the expenditures of this product. Once a vial of factor VIIa is reconstituted, it has limited stability. A dose-rounding policy was approved to try to decrease waste that occurs when NovoSeven® is ordered but not subsequently used. Once product is reconstituted, it is wasted if it is not used. By rounding doses to available vial sizes and reconstituting the vials immediately prior to use, unused doses will not be wasted. The table below will be used to adjust doses based on vial sizes.

RECOMBINANT FACTOR VIIa DOSE ROUNDING PROTOCOL

Actual Dose Ordered	Dose Dispensed to Nearest Vial Size	% Increase/Decrease
Less than 1 mg	Dispense as ordered	
1 mg – 1.79 mg	1.2 mg	20% ↑ – 33% ↓
1.8 mg – 2.99 mg	2.4 mg	33% ↑ – 20% ↓
3 mg – 4.19 mg	3.6 mg	20% ↑ – 14% ↓
4.2 mg – 5.39 mg	4.8 mg	14% ↑ – 10% ↓
5.4 mg – 6.59 mg	6 mg	10% ↑ – 8 % ↓
6.6 mg – 7.79 mg	7.2 mg	9% ↑ – 8% ↓
7.8 mg – 8.99 mg	8.4 mg	8% ↑ – 7% ↓
9 mg – 10.19 mg	9.6 mg	7% ↑ – 6% ↓