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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met August 16, 2011. 1 product was added in the *Formulary*, 5 were deleted, and 13 were designated nonformulary and not available. 2 interchanges were approved, while 5 criteria for uses were changed.

◆ ADDED

Nevirapine ER (Viramune® XR by Boehringer Ingelheim Pharmaceuticals)

◆ DELETED

Antibiotic Decontamination Solution (Compounded)*

Chloral Hydrate Liquid (Generic)*

Chloral Hydrate Suppositories (Generic)*

Muromonab CD3 (OKT3®)*

Simvastatin [80 mg] Tablets (Generic)*

**Nonformulary and not available*

◆ NONFORMULARY AND NOT AVAILABLE

Azficel (Laviv®)

Fentanyl Nasal Spray (Lazanda®)

Fidaxomicin (Dificid®)

Hydrocodone-Pseudoephedrine (Rezira®)

Hydrocodone-Pseudoephedrine-Chlorpheniramine (Zutripro®)

Indacaterol (Arcapta®)

Morphine [20 mg/mL] Liquid (Generic)

Phentermine (eg, Adipex-T® or Suprenza®)

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NEWS

New Florida law for controlled substances

Effective September 1, 2011, the State of Florida's new Prescription Drug Monitoring Program (PDMP) database was initiated. Any healthcare professional who dispenses a controlled substance is required to report information to the database within 7 days after *dispensing* the drug.

Florida's Prescription Drug Monitoring Program calls its database E-FORCSE, which stands for Electronic Florida Online Reporting of Controlled Substances Evaluation program. The PDMP was created in the 2009 session of the Florida legislature to encourage safer prescribing of controlled substances and reduce drug abuse and diversion within the state. Florida has received national attention for the large number of "Pill Mills" in the state, which has contributed to illicit prescription drug use throughout the country. Pill Mills are illegal clinics that prescribe controlled substances [primarily pain medications] without medical justification. These illicit prescription drugs are either misused and/or sold by the "patient."

The E-FORCSE database collects drug use histories for Schedule II, III, and IV controlled substances. These data will be accessible to prescribers and dispensers to help guide appropriate therapy and, hopefully, to decrease illicit use. According to reports, the state expects more than 100,000 prescribers and dispensers to upload information to E-FORCSE.

One concern with the database is confidentiality. The database complies with regulations for electronic protected health information consistent with the Health Insurance Portability and Accountability Act (HIPAA). Data will be included in the database only when the controlled substance is dispensed to the patient, not just prescribed. Healthcare providers do not have to report the administration of a controlled substance directly to the patient or if the amount is adequate to treat the patient during a treatment session. When the administration occurs at a hospital, nursing home, ambulatory surgery center, hospice, or intermediate care facility, it will not be listed in the database. Administration or dispensing a controlled substance to a patient under the age of 16 or a 1-time, 72-hour re-supply of a controlled substance are also not reported. Retroactive data from dispensers [covering January 1, 2011, to September 1, 2011] will be added in the E-FORCSE database by November 1, 2011.

Although these data are intended to help prescribers, there is no requirement that a prescriber access these data prior to writing a prescription for a controlled substance. Prescribers are encouraged to use this tool to improve patient care. In order to gain access, healthcare provides must apply to E-FORCSE. [At the time of writing this article, the direct link is not available.]

The intent of E-FORCSE is to reduce doctor shopping and prescription fraud by providing doctors and pharmacists a more complete controlled substance use history. It helps identify patients at risk for abuse or dependence so that they may receive the appropriate medical intervention. Most states have a similar prescription drug monitoring program. Law enforcement will have access to this database.

The implementation of the E-FORCSE monitoring program comes on the heels of several other changes in Florida law regarding controlled substances. The "Pill Mill Bill" had several additional measures intended to decrease the misuse of prescription controlled substances. Some aspects of this law include strict rules for the writing of prescriptions, including the requirements for pain-treatment plans and the

(continued on page 4)

Formulary update, *from page 1*

◆ INTERCHANGES

Atorvastatin (Lipitor®) 40 mg for **Simvastatin 80 mg**

Nitroglycerin 0.4 mg SL for **Nitroglycerin 0.3 mg SL**

◆ CRITERIA-FOR-USE CHANGES

Acetaminophen Oral Liquid and Drops†

Ferrous Sulfate Liquid†

Ibuprofen Liquid†

Potassium Chloride Liquid†

Prednisolone Liquid†

Sodium Chloride Liquid†

†Revised Pediatric Dose Rounding

Viramune® XR is an **extended-release (ER)** version of the non-nucleoside reverse transcriptase inhibitor (NNRTI) **nevirapine**, which is used in the management of patients infected with human immunodeficiency virus (HIV) or who have Acquired Immunodeficiency Syndrome (AIDS). The immediate-release (IR) version of nevirapine has been on the market since 1996. Viramune® XR was added in the *Formulary* to facilitate continuity of care between the outpatient and inpatient settings and to avoid any delay that might occur upon hospitalization. A delay in therapy could contribute to HIV resistance.

The ER formulation of nevirapine allows for once-daily dosing and decreases pill burden, which might be an advantage in the outpatient setting. Viramune® XR was approved based on the VERxVE and the TRANxITION trials. These trials are ongoing Phase 3 trials. The TRANxITION trial is scheduled to be finished collecting data for the primary outcome in December of 2011 and the VERxVE trial is scheduled to be finished collecting data on the primary outcome in September of 2011. The TRANxITION trial is an open-label trial with 443 subjects who were already taking nevirapine IR twice daily and had a viral load less than 50 copies/mL. The patients were randomized to Viramune® XR or nevirapine IR. At 24 weeks after randomization, 94% of IR group and 95% of the ER group continued to have a viral load less than 50 copies/mL. Both groups had a similar safety profile after 24 weeks as well. The VERxVE compared the efficacy and safety of Viramune® XR (n=505) and nevirapine IR (n=506) in 1011 treatment-naïve patients. At 48 weeks, 75% of the IR and 80% of the ER group had a viral load less than 50 copies/mL. Both treatment groups had a very similar safety profile at 48 weeks.

Viramune® XR carries the same warnings/precautions of hepatoxicity and fatal/non-fatal skin reactions as nevirapine IR. In addition, for nevirapine-naïve patients, a lead-in dose of 200 mg of nevirapine IR for 14 days is required before transitioning to Viramune® XR. To date, there are no data to support that Viramune® XR has any advantage over IR version of nevirapine, except for once-daily dosing. The results of the VERxVE and TRANxITION trials show that Viramune® XR is noninferior to nevirapine IR.

Compounded **antibiotic decontamination solutions** were deleted from the *Formulary* and designated nonformulary and not available based on a recommendation by the Anti-Infective Subcommittee. Selective decontamination of the digestive tract (SDD) is a practice that involves the administration of oral, non-absorbable antibiotics with or without systemic antibiotics to patients in order to eliminate pathogenic bacteria from their digestive tract selectively. Theoretically, these pathogens lead to infections in certain patient populations, such as those ventilated in the ICU or those undergoing a liver transplantation. Eliminating these pathogens would then reduce morbidity and mortality.

The practice was developed in the 1980s, and initial support came from numerous observational studies showing the practice to be of benefit. Since then, randomized controlled trials done in ICU patients have shown that the practice may be beneficial in that population. However, trials done in the setting of liver transplantation have not shown a benefit of this practice.

Further, the overuse of antimicrobials contributes to the growth of resistant pathogens, and there is no solid evidence for the benefit of SDD in patients undergoing a liver transplantation. Therefore, all versions of compounded antibiotic decontamination solutions were deleted from the *Formulary*.

Chloral hydrate is a sedative hypnotic that has been on the US market since the 1930s. Its use has decreased because of the availability of safer alternatives. When dosed appropriately, short-term use for procedural sedation can be safe; however, overdoses are difficult to manage and may be fatal. When used chronically, the sedative effect rapidly requires dosage escalations because of tachyphylaxis. The metabolite, trichloroethanol, can cause cardiotoxicity resulting in arrhythmias that are difficult to treat and do not respond to lidocaine.

The decision to delete chloral hydrate from the *Formulary* was based on a recommendation of the Medication Safety Committee to minimize the risk of difficult-to-treat overdoses. Chloral hydrate liquid is available in 5-mL cups (100 mg/mL), which requires nursing staff to measure doses at the bedside. This could contribute to the possibility of dose measurement errors. Chlorate is a Schedule IV controlled substance and patients may not use their own supply from home.

Muromonab CD3 was a murine monoclonal antibody to the CD3-antigen on the membrane of T-lymphocytes that inhibits lymphocyte function. It had labeled indications for the treatment of acute allograph rejection in renal transplant patients and for the treatment of steroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.

Centocor Ortho Biotech withdrew Orthoclone® OKT3 from the market because of the availability of multiple newer agents for the same uses. A 2008 Cochrane review concluded muromonab-CD3 provides no benefit over antithymocyte globulin (ATG) or anti-lymphocyte globlulin (ALG) in reversing rejection, preventing subsequent rejection, or preventing graft loss or death.

Simvastatin [80-mg] tablets were deleted from the *Formulary* and designated nonformulary and not available in order to promote safe use of this dosage form. The FDA recommends limiting the use of the highest approved dose of simvastatin (80 mg) because of increased risk of muscle damage with this dosage strength in some patients. This dosage strength was not taken off the market because some long-term patients who have been taking this dose may be able to continue this therapy. However, in the inpatient setting, the overall risks were determined to outweigh its continued use.

Patients taking simvastatin 80 mg daily have an increased risk of myopathy compared to patients taking lower doses or other drugs in the statin class. This risk appears to be higher during the first year of treatment, is often the result of interactions with certain medicines, and is frequently associated with a genetic predisposition toward simvastatin-related myopathy. The most serious form of myopathy, rhabdomyolysis, can damage the kidneys and lead to kidney failure, which can be fatal. The FDA required changes to the simvastatin label to add new contraindications (should not be used with certain medications) and dose limitations for using simvastatin with certain medicines.

The new changes to the drug labels for simvastatin-containing medicines

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Formulary update, *from page 2*
are based on the FDA's review of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial and other data described in the Agency's March 2010 ongoing safety review of high-dose simvastatin and increased risk of muscle injury. Simvastatin 80 mg should be used only in patients who have been taking this dose for 12 months or more without evidence of myopathy. Simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug. Patients ordered simvastatin 80 mg will be converted to atorvastatin 40 mg based on similar LDL lowering and less risk with the lower dose of atorvastatin.

Azficel-T is an autologous cellular product with a labeled indication for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults. This product uses a patient's fibrinoblasts that are grown in the laboratory and later injected into the patient's wrinkles. This cosmetic product has no role in the inpatient setting and was, therefore, designated nonformulary and not available.

Lazanda® is a nasal spray dosage form of fentanyl with a labeled indication for the management of breakthrough pain in cancer patients 18 years of age or older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. It has a black-box warning emphasizing its abuse potential, its risk in patients who are not opioid-tolerant, and that it is contraindicated in the management of acute or postoperative pain. It also has a strict Risk Evaluation and Management (REMS) program that includes lengthy instructions for use in the inpatient setting.

Lazanda® was designated nonformulary and not available. It is a Schedule II controlled substance and patients may not use their own supply from home when they are admitted to Shands. Per policy, the patient's supply will be sent home with a family member or stored with the patient's valuables until they are discharged.

Fidaxomicin is a novel, naturally occurring, macrocyclic antimicrobial used orally for the treatment of *Clostridium difficile* infection (CDI) in patients aged 18 and older. Fidaxomicin is a narrow-spectrum antibiotic active against aerobic and anaerobic Gram-positive bacteria, and exerts excellent activity against *Clostridium difficile*.

Fidaxomicin exerts its activity by inhibiting bacterial RNA polymerases. While fidaxomicin's mechanism of action is similar to rifamycins, cross-resistance has not been observed with rifamycins or other antibacterial agents. Fidaxomicin and its active metabolite demonstrate time-dependent killing of *C. difficile*. According to *in vitro* studies, the minimum inhibitory concentration in stool is well above the MIC of organisms studied. Mean systemic concentrations of fidaxomicin are unlikely to cause systemic adverse reactions.

Fidaxomicin is available as 200-mg tablets. The FDA-approved dose of fidaxomicin is 200 mg twice daily for 10 days for the treatment of CDI. No clinical trials have been completed or are ongoing for indications other than management of CDI.

Fidaxomicin has been shown to be equal in efficacy to vancomycin in a Phase III clinical trial for the treatment of primary CDI. Initial cure rates were similar between fidaxomicin and vancomycin (92.1% vs. 89.8% respectively, per-protocol analysis). Rate of CDI recurrence favored fidaxomicin (13.3% vs. 24.0% vancomycin, per-protocol analysis, P=0.005; NNT=10), though this was only seen with non-epidemic (non-NAP1/BI/027) strains of *C. difficile*. One theory for decreased recurrence is fidaxomicin's decreased efficacy against the intestinal bacteria *Bacteroides* spp. compared to vancomycin. This results in no net change in colony counts of Bacteroides spp. in the stool in patients treated with fidaxomicin, whereas oral vancomycin results in a significantly lower colony count. Experts believe this quality may contribute to prevention of overgrowth of *C. difficile*.

The acquisition cost of a 10-day treatment course of CDI with fidaxomicin 200 mg twice a day is nearly $3000. The cost of a 10-day course of vancomycin compounded liquid 125 mg 4 times a day is less than $20 and a 10-day course of metronidazole 500 mg 3 times a day is less than $5.

Because of the prohibitive cost and benefit only in certain patient populations, more information is needed before fidaxomicin can be recommended for wide utilization in practice. Therefore, fidaxomicin was designated nonformulary and not available. A treatment protocol for the management of CDI will be developed to determine where the various options (vancomycin, metronidazole, nitazoxanide, rifaximin, fidaxomicin) fit in the management of various clinical scenarios.

Rezira® and **Zutripro**® are hydrocodone-containing drugs recently approved with labeled indications for the treatment of cough and nasal congestion associated with the common cold. Zutripro® also has a labeled indication for cough associated with nasal allergies.

Hydrocodone is an opioid that is used as an analgesic and antitussive. It is not listed in the *Formulary*. Since it is a controlled substance, patients may not use their own supply from home.

Pseudoephedrine and chlorpheniramine are listed in the *Formulary.* Patients admitted on Rezira®, Zutripro®, or other hydrocodone-containing products for cough will be guided towards dextromethorphan, which is the antitussive listed in the *Formulary.* Rezira® and Zutripro® were designated nonformulary and not available and patients may not use their own supply from home.

Indacaterol is a long-acting beta$_2$-adrenergic agent available as a powder in a capsule that is inhaled using a special device (Neohaler®). It has a labeled indication for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including bronchitis and/or emphysema.

Indacaterol was designated nonformulary and not available, but patients may use their own supply from home. There are published studies comparing 150 mcg daily of indacaterol with salmeterol 50 mcg twice a day; however, the approved dosage for indacaterol is 75 mcg daily. A dosage of salmeterol 50 mcg twice a day is a reasonable dosage alternative and is recommended in EPIC.

Another high-concentration of **oral morphine (20 mg/mL)** was recently approved by FDA. This strength of oral morphine solution has a labeled indication for the management of moderate-to-severe acute and chronic pain where an opioid analgesic is appropriate. It has a black-box warning stating that morphine sulfate oral solution is available in multiple concentrations and that the 20-mg/mL concentration is indicated for use only in opioid-tolerant patients. Errors confusing the 20-mg/mL concentration with lower concentrations (2 mg/mL) could lead to serious 10-fold overdoses and deaths. For this reason, the 20-mg/mL oral morphine solution was designated nonformulary and not available.

Phentermine (eg, Fastin®, Adipex-P®) is a sympathetic amine with anorectic properties with a labeled indication for the short-term adjunctive use in a weight reduction regimen that includes exercise, behavioral modification, and caloric restriction in patients with a BMI greater than 30 or a BMI greater than 27 with other risk factors (eg, diabetes). **Suprenza**® is a new orally disintegrating tablet (ODT) form of phentermine. No dosage forms of phentermine have been listed in the *Formulary.* These products are controlled substances

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News, *from page 1*
use of counterfeit-proof prescription pads purchased from state-approved vendors. Pharmacists must now report to police an attempt to purchase drugs fraudulently or face criminal prosecution.

These laws will have several important ramifications at Shands at UF. Most importantly, physicians who prescribe controlled substances, particularly for pain, will need to be familiar with these new laws that put limits on these practices. These laws create new administrative penalties for doctors who "overprescribe narcotics" and violate standards of care.

LINKS:

1. http://drugcontrol.flgov.com/pdmp/index.html

2. http://www.doh.state.fl.us/mqa/PDMP/docs/Fact%20Sheet-Health%20Care%20Practitioners.pdf

3. http://www.hidinc.com/flpdmp

Formulary update, *from page 3*
and, thus, patients may not use their own supply from home. Because these drugs are not necessary when a patient is hospitalized and could complicate a patient's management, all dosage forms of phentermine were designated nonformulary and not available.

Sublingual (SL) nitroglycerin (NTG) is a vasodilator used in the management of angina and for an acute myocardial infarction. During initial recognition and management of myocardial infarct, guidelines for the treatment of ongoing ischemic discomfort by the American College of Cardiology and American Heart Association (ACC/AHA) state a patient should receive SL NTG (0.4 mg). Nitrates should not be administered if systolic blood pressure (SBP) is less than 90 mmHg, or greater than 30 mmHg below baseline, severe bradycardia (less than 50 bpm), tachycardia (greater than 100 bpm), or suspected RV infarction. This recommendation highlights a source that contains a recommended dose of SL nitroglycerin [most do not]. This suggests that 0.4 mg of SL nitroglycerin is the most common strength.

Prior to the implementation of EPIC, the 0.4-mg dose of SL NTG was used primarily and was widely available throughout the hospital. Now the 0.3-mg SL dose is occasionally ordered, presumably because of continuation of what the patient was receiving at home. The lack of availability of this dosage form could have contributed to a delay in treatment.

For the treatment of acute angina, it is recommended to initiate the lowest dose (0.3 mg) of SL NTG in geriatric patients, as they are more sensitive to the hypotensive and bradycardic effects of nitroglycerin. Considering patients are in the hospital, where blood pressures and heart rates are routinely monitored, the P&T Committee determined that it is reasonable to **interchange SL NTG 0.3 mg to 0.4 mg**.

The dose-rounding policy was revised for several drugs, including **acetaminophen oral liquid** and **drops**, **ferrous sulfate liquid**, **ibuprofen liquid**, **potassium chloride liquid**, **prednisolone liquid**, and **sodium chloride liquid**. These changes were made to be consistent with what is ordered in EPIC, to be consistent with Shands Jax, and to round doses to the nearest standard dose. Please refer to Pharmacy Policy 06-05-39 *Automatic Route and Dosage Changes* for the entire policy, which is available on the Shands at UF Portal.