FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met June 15, 2010. 6 products were added in the Formulary, and 3 products were deleted. 19 products were designated nonformulary and not available. 5 interchanges and 1 standard concentration was approved. 1 drug was evaluated, but no action taken.

◆ ADDED

Doripenem* (Doribax® by Ortho McNeil)
*Effective August 1, 2010

Efavirinz-Emtricitabine-Tenofovir (Atripla® by Bristol Myers Squibb)

Epirubicin (Generic)

Etravirine (Intelence® by Centocor Ortho Biotech)

Pancrelipase (Pancreaze® by Ortho-McNeil)

Pancrelipase (Zenpep® by Eurand Pharmaceuticals)

◆ DELETED

Imipenem-Cilastatin (Primaxin®)†

Pancrelipase† (Ultrase® by Axcan Pharma)

Pancrelipase† (Viokase® 8 by Axcan Pharma)

†Nonformulary and not available

◆ NONFORMULARY AND NOT AVAILABLE

Beclomethasone Nasal Spray (Beconase®)

Budesonide Nasal Spray (Rhinocort®)

Bupropion Immediate-Release (Wellbutrin®)

Bupropion Extended-Release (Wellbutrin® XL)

(continued on next page)
Doripenem is a carbapenem antibiotic with a broad spectrum of activity against aerobic and anaerobic gram-positive and gram-negative bacteria including *Pseudomonas aeruginosa*. Doripenem is labeled for use in complicated urinary tract infections, including pyelonephritis, and complicated intra-abdominal infections. It has also been evaluated in nosocomial pneumonia, including ventilator-associated pneumonia, and isoniazid-resistant tuberculosis. Doripenem has been shown to be non-inferior to levofloxacin for complicated urinary tract infections, meropenem for complicated intra-abdominal infections, piperacillin-tazobactam for nosocomial pneumonia, including early onset ventilator-associated pneumonia, and imipenem-cilastatin for ventilator-associated pneumonia. In addition, it has been shown to be less likely to select for carbapenem resistant pseudomonas isolates. Most data are *in vitro*, but when compared to imipenem-cilastatin in patients with pseudomonas pneumonia, doripenem resulted in fewer resistant isolates.

Doripenem is contraindicated in patients with a hypersensitivity to other carbapenems or who have had an anaphylactic reaction to other beta-lactam agents. Like other carbapenems, administration of doripenem with valproic acid or sodium valproate results in decreased serum valproic acid concentrations and may lead to seizures in patients using these drugs for seizure control. In addition to this reaction with valproic acid, carbapenems as a class have been shown to increase the risk for seizures. The risk appears to be greatest with imipenem-cilastatin, and recent evidence suggests that meropenem and doripenem have a relatively low propensity to induce seizures. Most other adverse events with doripenem are mild, though there have been post-marketing reports of anemia, thrombocytopenia, neutropenia, toxic epidermal necrolysis, and Stevens-Johnson Syndrome.

The recommended adult dose for doripenem is 500 mg IV every 8 hours; each dose should be given over 1 hour. The dosage is adjusted in patients with decreased renal function. There is no dosage adjustment needed in patients with hepatic impairment. The cost per day for doripenem is 25% less expensive than other agents listed in the Formulary. The dosage is adjusted in patients with decreased renal function. There is no dosage adjustment needed in patients with hepatic impairment. The cost per day for doripenem is 25% less expensive than other agents listed in the Formulary.

Based on adequate clinical data from common infections seen at Shands at UF, improved potency against imipenem-cilastatin isolates (30% of pseudomonas isolates resistant to imipenem-cilastatin may be susceptible to doripenem), the potential for an improved safety profile, and the possibility of generating fewer carbapenem-resistant isolates, doripenem was added in the Formulary and restricted to Infectious Diseases approval with criteria consistent with other carbapenems. After supplies are depleted, imipenem-cilastatin will be nonformulary and not available; meropenem’s criteria for use were changed to the treatment of resistant organisms in pediatric patients and bacterial meningitis.

Atripla® contains a fixed-dose combination of 3 drugs: efavirenz (a non-nucleoside reverse transcriptase inhibitor [NNRTI]), emtricitabine (a nucleoside analog reverse transcriptase inhibitor [NRTI]), and tenofovir disoproxil (a nucleoside analog reverse transcriptase inhibitor [NRTI]). Atripla® is intended to provide combination antiretroviral therapy for administration as a once-daily tablet for the treatment of HIV-1 infected adults. The fixed combination aims to simplify regimens and improve adherence to therapy.

The goal of antiretroviral therapy for HIV-1 infection is to delay disease progression and increase the duration of survival by achieving maximal and prolonged suppression of HIV-1 replication. The standard of care for treatment involves the use of a combination of at least 3 antiretroviral agents. Unfortunately, antiretroviral regimens can have a high pill burden and have a frequency of administration that interferes with quality of life. Furthermore, successful long-term treatment requires complete adherence to minimize the impact of increasing drug resistance. Therefore, there continues to be a need for new treatments that combine potent and sustained efficacy with acceptable tolerability and minimal long-term toxicity, as well as practical and convenient dosing regimens.

Atripla® has been evaluated in 2 clinical evaluations. Study 934 compared the efavirenz, emtricitabine, and tenofovir combination to zidovudine-lamivudine and efavirenz in 511 treatment-naive HIV patients. At study end, patients could be converted to Atripla® and were evaluated for continued viral suppression at 48 weeks. At 144 weeks (prior to switch), 71% and 58% patients were classified as responders, respectively. Following 144 weeks, 286 patients who responded to previous therapy were switched to Atripla®. Maintenance of viral suppression at 48 weeks was achieved in 94% and 90% of patients, respectively. In study 073, 300 virologically suppressed patients were randomized in a 2:1 fashion to receive Atripla® or maintain the current regimens for 48 weeks. Following randomization, patients were switched to either Atripla® or maintained on their previous regimens; viral suppression was maintained in 89% and 88%, respectively.

Adverse events with Atripla® are consistent with its individual components. Boxed warnings include lactic acidosis, renal failure, renal insufficiency, elevated creatinine, hypophosphatemia, Fanconi syndrome, and hepatitis B exacerbations following discontinuation of the product. Additional adverse effects include dizziness, nausea, and abnormal dreams.

Overall, Atripla® has been found to be safe and effective. In order to avoid delays in appropriate therapy and minimize the risk of antiviral resistance, Atripla® was added in the Formulary.

Epirubicin is an anthracycline chemotherapy agent with activity
**Formulary update, from page 2**

Similar to doxorubicin. Epirubicin has a labeled indication for use as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection in the treatment of primary breast cancer. It is also used off-label in combination with other agents for many solid tumors.

Epirubicin works by intercalating into the DNA and halting protein synthesis. This causes topoisomerase II to cleave the DNA. The enzymatic activity of helicase is inhibited and the cell is unable to repair the DNA damage. Epirubicin also forms free radical complexes when it forms a compound with metal ions in the cell.

Epirubicin is available for IV administration and is rapidly distributed throughout tissues. It is heptatically cleared and has a shorter plasma half-life compared to doxorubicin. Depending on the type of cancer, the total dose for a cycle of chemotherapy of epirubicin ranges from 75 mg/m² to 120 mg/m².

Few trials compare epirubicin to doxorubicin for soft tissue sarcoma. Mouridsen and colleagues reported that epirubicin has similar efficacy with lower toxicity, but the dosages used were not therapeutically equivalent. The major dose limiting toxicity is myelosuppression. In addition, almost all patients will experience alopecia. Gastrointestinal irritations and injection site reactions are also commonly reported adverse effects.

Epirubicin is more expensive than doxorubicin. However, doxorubicin may cause more cardiomyopathy, which could lead to future medical problems and increase the overall costs associated with its use. Epirubicin was added to the formulary based on the potential for less adverse effects and previous clinical trials that have shown success in breast cancer and soft tissue sarcomas.

**Etravirine** is a non-nucleoside reverse transcriptase inhibitor (NNRTI). NNRTI-based regimens are a mainstay in managing patients with HIV-1 infection. A major challenge for this class of antiretroviral agents is the development of resistance, which affects the entire NNRTI class.

Etravirine is a second-generation NNRTI. It has been shown to have activity against both wild type and NNRTI-resistant isolates. With the development of this product, clinicians were provided with an additional tool for managing treatment experienced patients. Etravirine is an option for the management of treatment experienced HIV-1 patients.

Etravirine was evaluated in 2 clinical trials (DUET-1 and DUET 2). Patients were randomized to receive darunavir-ritonavir, the best available backbone regimen, and either etravirine or placebo. Following randomization, the proportion of patients achieving undetectable viral loads by week 96 were 57% in the etravirine group and 36% in the placebo group. Furthermore, the virological response was durable, with 91% of patients attaining a viral load less than 50 copies/mL at 48 weeks and continuing to have undetectable viral load at week 96.

Etravirine was generally well tolerated and adverse events were comparable between groups, with the exception of rash, which occurred in 21% of the etravirine group versus 12% in the placebo group. Rash consistently appears more frequently in the etravirine group versus placebo. In addition, etravirine’s prescribing information has been modified to include post-marketing reports of toxic epidermal necrolysis and hypersensitivity reactions. Monitoring for skin reactions is recommended.

PancrEnzapase is a mixture of the pancreatic enzymes lipase, protease, and amylase. Although pancrEnzapase products have been on the market for decades, they have been unapproved drugs. The FDA issued a mandate in 2004 requiring manufacturers of pancreatic enzyme replacement products to seek approval through the NDA process. There have been concerns about the lack of standardization and equivalency. In Florida, pancrEnzapase is listed in the Negative Formulary.

Products listed in the Shands at UF Formulary included Viokase® powder, Viokase® 8 tablets, Creon® 6000 capsules, and Ultrase MT (12, 18, and 20) capsules. Of these products, only Creon® currently has FDA approval. The pancrEnzapase products currently approved by the FDA include Zenpep®, Creon®, and Pancreaze®.

Viokase® has been shown to decrease postprandial gastric 3-hour acid secretion and decrease the number of patients with not more than 20% of the number of mepivacaine-positive patients. In this study, there is no approved non-enteric-coated product on the market.

Although there was no recall of currently marketed products, manufacturers of unapproved products have ceased sales and supplies are limited. Florida Medicaid no longer pays for unapproved pancrEnzapase products, which limits their outpatient use.

The P&T Committee approved an interchange of pancrEnzapase products that results in lipase doses that do not change by more than 20%. Creon® 6000 is available for small children because the bead size is the smallest. The capsules can be opened and the contents sprinkled on food. The lowest dose of Pancreaze® (4200 unit) is also listed in the Formulary. All doses of Zenpep® are listed and higher pancrEnzapase doses will be converted to the closest dose of Zenpep®.

Beclomethasone, budesonide, ciclesonide, flunisolide, and triamcinolone nasal sprays were all designated non-formulary and not available and will be interchanged to fluticasone nasal spray. Mometasone nasal spray had already been designated nonformulary and not available and interchanged to fluticasone nasal spray. These changes will be based on low doses, which will be converted to 1 spray of fluticasone in each nostril once a day, or high doses, which will be converted to 2 sprays in each nostril once a day. It is generally accepted that nasal steroids are equivalent at equivalent doses. Only 2 of these agents are available as generics, fluticasone and flunisolide, and fluticasone is more common. Therefore, it was selected as the only nasal steroid listed in the Formulary.

If patients have their own inhaler from home and do not wish to be changed to fluticasone, that is allowable; however, beclomethasone, budesonide, ciclesonide, flunisolide, mometasone, and triamcinolone nasal sprays will not be purchased for inpatient use.

**Bupropion** is an antidepressant unrelated to other antidepressants. It is also used for smoking cessation.

There are multiple forms of bupropion on the market. Bupropion hydrobromide (Wellbutrin®) immediate-release (IR) was first approved in 1995 and has been available as a multi-source generic product for many years. The 3-times-a-day dosing of the IR product resulted in conversion, in most circumstances, to an extended-release product. An “SR” form of bupropion (Wellbutrin® SR) was marketed as a twice-a-day antidepressant and Zyban® (another twice-a-day form of bupropion) was marketed for smoking cessation. Generic bupropion SR has been marketed for several years. The once-daily form of bupropion (Wellbutrin® XL) was marketed in 2003; it too is now available as a generic.

Aplenzin® is an extended-release of bupropion hydrobromide, which was approved by the FDA in April 2008. Aplenzin® only has a labeled indication for the treatment of major depressive disorder. Aplenzin® is given once daily in the morning, similar to Wellbutrin® XL.

The various salts and dosage forms of bupropion will now be interchanged to a generic “SR” dose. The SR dosage form was chosen over the “XL” dosage form because some patients, particularly children at Vista, require dosage titration before low dosages. The “XL” dosage form was not an option for these patients. In the interest of safety, it was determined that having only 1 dosage form (ie, not both SR and XL) would be the least likely to result in dispensing errors.

Doses of bupropion 50-mg (½ 100-mg), 75-mg (½ 150-mg), 100-mg (continued on next page)
150 mg, and 200 mg tablets will be used. The last dose per day will be administered at 1600 (ie, 0900-1600 or 0800-1200-1600) to avoid insomnia from the stimulant effect of bupropion. The ½-tablets (ie, 50-mg and 75-mg) are not scored, thus, will be absorbed more like the IR dosage form.

**Vimovo®** is a fixed combination of esomeprazole [Nexium®] 20 mg and naproxen [generic] 325 or 500 mg with a labeled indication for the treatment of pain in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. The esomeprazole is present to decrease the risk of developing NSAID-associated gastric ulceration.

**Vimovo®** was designated nonformulary and not available. Esomeprazole is not listed in the Formulary and is nonformulary and not available. If **Vimovo®** is ordered, the prescriber will be contacted to switch the patient to naproxen and a proton pump inhibitor listed in the Formulary.

**Sprix®** is a nasal spray formulation of ketorolac approved for the short-term (up to 5 days) management of acute moderate to moderately severe pain. Ketorolac nasal spray was designated nonformulary and not available. There are other options for the inpatient use of nonsteroidal anti-inflammatory drugs (NSAIDs) including ketorolac IV or IM and other NSAIDS given orally (eg, ibuprofen or naproxen).

**Extended-release metformin** (eg, Glucophage® XL and Fortamet™) is a frequently used nonformulary drug. Metformin is an oral antidiabetic agent that is a first-line agent for the treatment of type 2 diabetes. It is effective, relatively safe, and the generic immediate-release product is inexpensive.

The daily metformin ER dose is given once a day with the evening meal. Immediate-release (IR) metformin is given once, twice, or even three times daily with meals. According to the metformin ER labeling, an equal daily dose can be used to transition from the IR to the ER dosage form. Thus, the converse should also be acceptable.

Although there are some claims that the ER dosage form has fewer gastrointestinal (GI) adverse effects, this is based on indirect comparisons of placebo-controlled studies. Multiple head-to-head studies between the IR and ER dosage forms show the GI effects are similar.

Metformin ER will now be nonformulary and not available and will be interchanged to metformin IR. For 750-mg dose increments of metformin, 850-mg doses of the IR will be used.

**Natazia®** is an oral contraceptive containing estradiol valerate and estradiol valerate with dienogest. Estradiol is an estrogen and dienogest is a progesterone. Throughout the month, the amount of dienogest varies from zero to 3 mg. **Natazia®** is a 4-phasic oral contraceptive.

**Natazia®** was designated nonformulary and not available. Patients can use their own supply from home, which is common for the various oral contraceptives that patients may be taking.

Only 1 combination oral contraceptive is listed in the Formulary, ie, a generic version of Lo/Ovral®. The generic Lo/Ovral® (containing ethinyl estradiol and norgestrel) is available for patients with acute, heavy uterine bleeding due to anovulatory cycling, ITP, or acute leukemia.

When an order for a nonformulary oral contraceptive is written, the pharmacist will call the nursing floor to determine whether the patient has her own supply. This home medication can be used according to existing policy, which requires a written order specifying the oral contraceptive and daily dosage. If a patient does not have her own supply and the prescriber wants to continue an oral contraceptive during the patient’s
hospitalization, a generic equivalent of Lo/Ovral® will be recommended. The patient can resume their home oral contraceptive upon discharge.

**Invega Sustenna®** is an extended-release injectable dosage form of the atypical antipsychotic paliperidone. Paliperidone is the active metabolite of risperidone. Oral paliperidone is currently nonformulary and not available, and now Invega Sustenna® is nonformulary and not available.

**Sipuleucel-T** is an autologous cellular vaccine used for the treatment of prostate cancer. It has a labeled indication for the treatment of patients with asymptomatic or minimally symptomatic, metastatic, androgen-independent prostate cancer.

Sipuleucel-T costs $31,000 per infusion. Each patient receives 3 infusions at 2-week intervals. Thus, the total cost of therapy is $93,000. Sipuleucel-T was designated nonformulary and not available for inpatient use, but will be available for selected patients in the outpatient setting.

A generic version of **Ultram® ER** was approved. **Tramadol ER** (brand and generic) was designated nonformulary and not available and will be automatically interchanged to tramadol immediate-release (IR). Tramadol ER products will be switched to tramadol IR by taking the total daily dose of the ER and giving the IR 4 times a day (rounded to the nearest available dosage form).

A **compounded ophthalmic drop** that goes by the acronym ADAA, which stands for Anesthetic, Dilating, Antibiotic, Anti-Inflammatory, was evaluated for possible addition in the Formulary. The ingredients include lidocaine (anesthetic), phenylephrine (dilating), tropicamide (dilating), cyclopentolate (dilating), moxifloxacin (antibiotic), and ketorolac (anti-inflammatory).

This mixture was requested for use pre-operatively before cataract surgery. Instead of using individual drops, this mixture supposedly decreases costs, is easier to use, and saves time. Each of these individual ingredients are currently listed in the Formulary, except ketorolac ophthalmic.

This product could not be obtained from a compounding pharmacy. In order not to be manufacturing, the product would have to be made on a patient-specific basis with a prescription provided ahead of time, which is not practical.

In order to be compounded at Shands, stability data need to be available, which are currently not available. Thus, this compounded product was not considered for listing in the Formulary.

**Arginine powder** is not listed in the Formulary and is not available because it is a nutritional supplement, not a drug. In patients who need oral arginine supplementation, the IV formulation is used orally. The confusion about what dosage forms are acceptable could result in a delay in therapy. Therefore, the P&T Committee approved an automatic interchange from arginine powder to the IV solution given orally.

Arginine supplementation is used in rare genetic disorders that impair the formation of arginine. These urea-cycle disorders result in hyperammonemia, if not treated with arginine.

**Terbutaline** is a beta-adrenergic receptor agonist. Although originally used as a bronchodilator, it is often used off-label as a tocolytic for the prevention of preterm labor. It is also used IV for the treatment of status asthmaticus in children.

There was no standard concentration for terbutaline at Shands at UF. Therefore, a 1-mg/mL terbutaline solution was added to both the Adult and Pediatric Standard IV Concentration Lists.
which became available as a generic in 2009, Prilosec® still made the top 10 brand list, but its sales decreased 24% compared with the previous year as a generic version became available.

Probably the biggest surprise in the top generics list is an opioid containing drug (ie, hydrocodone with acetaminophen or generic “Vicodin®”) is, by far, the #1 drug prescribed in terms of volume (brand or generic). There were 3 times as many prescriptions for hydrocodone-acetaminophen as the top brand name drug, Lipitor®.

Oxycodone with acetaminophen is #18 with 27,238,000 prescriptions. Another controlled substance, alprazolam (generic Xanax®) was #9 with 44,467,000 prescriptions dispensed. Although ranked number 8 in terms of dollars spent, brand name OxyContin® was #41 in terms of volume with 4,498,000 prescriptions costing $309,784,000. Crestor® accounted for 18,430,000 prescriptions and $366,706,000, and lovastatin (#36 with 17,827,000 prescriptions and costing $1,093,570,000) pravastatin (#38, 79,000,000 prescriptions) include simvastatin (#3 terms of number of generic prescriptions with 72,966,000 and costing $1,184,292,000), panto prazole (#16), and now lansoprazole, which became available as a generic in 2011.

Although not making the top 10 list in terms of dollars, brand name albuterol inhalers were among the fastest growing prescription drugs (in terms of number of prescriptions). Prescriptions for ProAir® HFA (#6 in volume of brand prescriptions with a 59% increase), Ventolin® HFA (#30 with a 303% increase), and Proventil® HFA (#46 with a 7% increase) increased. Prescriptions for albuterol used to be relatively inexpensive when they used chlorofluorocarbon (CFC) propellants. However, the Clean Air Act phased out CFC-containing drugs in 2009 and the hydrofluorocarban (HFA) propellant albuterol products are no longer available as generics. The more expensive brand products do not deplete the ozone, but they might deplete patients’ wallets. Patients’ copays often went from as low as $4 to $30 or more as the total costs dramatically increased.