

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met September 18, 2012. 8 products were added in the *Formulary*, and 2 were deleted. 6 products were designated non-formulary and not available and 2 interchanges were approved. Several drug use criteria were updated or established.

◆ ADDED

Bacillus-Calmette-Guerin Intravesical Injection (Tice® BCG)

Dextromethorphan Liquid 15 mg/5 mL (Generic)

Febuxostat (Uloric®)*
*Restricted: continuation of home therapy

Lactrodectus Mactans Antivenin (Black Widow Spider Antivenin)†
†Expiration dating extended beyond the labeling

Sildenafil Injection (Revatio® IV)*
*Restricted: children undergoing diaphragmatic hernia repair

Sipuleucel-T (Provenge®)*
*Restricted: Infusion Center only

Topical Thrombin, Recombinant (Recothrom®)

Zinc Injection (Generic)

◆ DELETED

Bacillus-Calmette-Guerin Intravesical Injection (TheraCys®)‡
‡Nonformulary and not available

Topical Thrombin, Bovine (Thrombin JMI®)‡
‡Nonformulary and not available

◆ NONFORMULARY AND NOT AVAILABLE

Ipratropium and Albuterol Spray (Combivent® RespiMat®)

Locaserin (Belvic®)

Mirabegron ER (Myrbetriq®)

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ADVERSE DRUG REACTIONS

Oral Contraceptives and Thromboembolic Risk

Oral contraceptives (OCs), commonly prescribed in the United States, are vital for public health, by preventing unwanted pregnancy, as well as personal health, by preventing cancer, treating acne and endometriosis, and relieving menstrual disorders.

The warnings, contraindications, precautions, adverse reactions, and risks mandated in Food and Drug Administration (FDA) labeling may create a distorted, unbalanced public image of these products as the rare risks are emphasized over the overwhelming benefits.

In December of 2011, the FDA convened a panel to address the increase in reported incidence of venous thromboembolisms (VTEs) with newer OC formulations.¹ The culprits were thought to be the new generation of progestins (desogestrel, etonogestrel [ETON], gestodene or norelgestromin [NGMN]) or an antiandrogen (drospirenone [DRSP]) contained in these products.

In response, the FDA funded a retrospective, cohort study to evaluate both the risk of thrombotic and thromboembolic events associated with OCs.² The study compared OC formulations

containing DRSP, NGMN, and ETON individually to comparator products (COMP), containing an older progestin (levonorgestrel, norethindrone, or norgestimate) with ethinyl estradiol (EE).² The risk of VTE with DRSP, NGMN, and ETON was significantly higher compared with COMP among all users (HR 1.7, 1.6, and 1.6, respectively).² These findings translate into an estimated 9.8 to 11.9 VTEs per 10,000 person-years (PYs) with these relatively novel products compared to 6.0 events per 10,000 PYs with the comparator formulations.² Of note, the incidence was slightly higher overall among new users compared to all users.² Specifically, the risk of atherothrombotic events (adjusted for hypertension, hyperlipidemia, and diabetes) was significantly increased among new users on DRSP compared to those on COMP products [HR (95% CI), 2.0 (1.1 – 3.8)].²

A comprehensive review of the literature, including 9 trials involving DRSP-containing products and 4 involving the NGMN-containing patch, suggests a wider range of VTE occurrence, between 2.3 to 13 events per

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NEWS

Medication Safety Subcommittee

The Medication Safety Committee was formed in August of 1999. At that time, it was a subcommittee of the Risk Management Committee, which was chaired by the Chief of Staff. The Medication Safety Committee has always had indirect reporting to the P&T Committee, particularly when drug policy or formulary changes were needed based on medication safety findings.

When the Institute for Safe Medication Practices evaluated Shands UF last year, they recommended that the Medication Safety Committee become a subcommittee of the P&T Committee and that it have a formal charter. The

Medication Safety Subcommittee will now routinely report to the medical staff via the Pharmacy and Therapeutics Committee.

The Pharmacy and Therapeutics Committee is the medical staff committee that serves as the formal line of communications between the hospital and the medical staff on all drug-related matters.

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◆ **NONFORMULARY AND NOT AVAILABLE**

Phentermine and Topiramate (Qsymia®)

◆ **INTERCHANGES**

Combivent® Aerosol for Combivent® Respimat® §
§Interchanged to Combivent® Aerosol: 2 inhalations for 1 spray

Tolterodine ER (Generic) for **Mirabegron ER** (Myrbetriq®) §
§Tolterodine ER 2 mg for Mirabegron ER 25 mg and 4 mg for 50 mg

◆ **CRITERIA-FOR-USE CHANGES**

Antihemophilic Factor, Recombinant (Advate, Recombinate®, and Xyntha®)¶
¶Patients may use their own supply; Helixate-FS® is identical to Kogenate-FS® marketed by a different company

Carfilzomib (Kyprolis®)*
*Added in the Chemotherapy Policy

Doripenem (Doribax®)*
*Restricted

Influenza Vaccine (Fluarix® and Fluzone®)

Meropenem (Generic)*
*Designated as the preferred carbapenem

Nebivolol (Bystolic®)**
**Nonformulary and not interchanged

Ondansetron Injection (Generic)*
*Maximum dose of 16 mg (0.15 mg/kg up to 16 mg in children) every 4 hours

Prothrombin Complex Concentrate (Profilnine® SD)*
*Up to 10% dose rounding approved.

Vincristine Liposomal (Marqibo®)*
*Added in the Chemotherapy Policy

Ziv-aflibercept (Zaltrap®)*
*Added in the Chemotherapy Policy

Bacillus-Calmette-Guerin injection is an intravesical live dosage form of *Bacillus-Calmette-Guerin* (BCG) strains of attenuated *Mycobacterium bovis*. There is a shortage of TheraCys®, which has been listed in the *Formulary*. Since TheraCys® is expected to be unavailable until late 2013, **Tice® Intravesical BCG** will be used as an alternative to TheraCys®. TheraCys® is reportedly not being marketed currently because of quality control issues.

Intravesical BCG has been administered in the bladder for the treatment of carcinoma *in situ* of the urinary bladder. It also has been used for prophylaxis of primary or recurring stage T_a or T₁ papillary tumors following transurethral resections (TURPs).

BCG promotes a local acute inflammatory and sub-acute granulomatous reaction with macrophage and lymphocyte infiltration in the urothelium and lamina propria of the urinary bladder. The anti-tumor effect appears to be T-lymphocyte dependent.

Dextromethorphan liquid was added in the *Formulary* as a single agent. Dextromethorphan has traditionally been used as an antitussive and is in many cough remedies labeled "DM." Dextromethorphan has long been listed in the *Formulary* in combination with guaifenesin.

Dextromethorphan is chemically related to opioids, but does not stimulate opioid receptors. It is a N-methyl-D-aspartate (NMDA)-receptor and sigma-1 agonist. It is rapidly absorbed and it is metabolized by CYP2D6 and CYP3A4. Dextromethorphan may cause drowsiness, dizziness, and fatigue.

Dextromethorphan has been studied for pain relief with mixed results. Some compendia list the evidence to support its use for pain as inconclusive. It has also been used for its neuroprotective effects after central nervous system (CNS) injuries. The data to support this use are not convincing.

Febuxostat is a xanthine oxidase inhibitor with a labeled indication for the chronic management of hyperuricemia in patients with gout. It works like allopurinol, which is also a xanthine oxidase inhibitor. The labeling states that febuxostat is 25% to 35% more effective than allopurinol at lowering uric acid levels to less than 6 mg/dL. Unfortunately, a higher rate of cardiovascular thrombotic events has been observed.

Febuxostat is titrated to achieve serum urate concentrations of less than 6 mg/dL, levels that have been shown to lower the risk of gout flares. Febuxostat is available in 40- and 80-mg oral tablets. It is recommended that patients start on 40 mg of febuxostat daily. If after 2 weeks, a serum urate level less than 6 mg/dL is not reached, the patient's dose may be increased to 80 mg per day.

The efficacy of febuxostat versus allopurinol at reducing serum urate concentrations to therapeutic levels has been proven by several randomized clinical trials. Though febuxostat was often found to lower uric acid concentration more than allopurinol, no significant differences have been detected in clinical outcomes.

Since febuxostat has a higher incidence of cardiovascular and thromboembolic events than allopurinol, patients should be monitored for signs and symptoms of myocardial infarction or stroke. FDA has mandated phase-IV clinical trials for cardiovascular safety of febuxostat.

The acquisition cost for a daily dose febuxostat is approximately 60 times higher than that for allopurinol.

Febuxostat was added in the *Formulary*, but its use is limited to patients admitted on febuxostat. Starting patients on febuxostat in the inpatient setting could be problematic.

Inability to afford the cost or copays for this expensive drug could delay a patient's discharge or result in therapy being stopped. Third-party payers may require patients to either fail allopurinol or have a contraindication to allopurinol before covering febuxostat. Further, starting febuxostat in the inpatient setting could trigger an acute gout attack.

Lactrodectus mactans antivenin is better known as black widow spider antivenin. The FDA recently extended the expiration date of Merck's black widow spider venom because this product is on shortage and is difficult to obtain. The product has been shown to be stable, even though it may be beyond its expiration date. Although black widow spider antivenin has long been stocked at Shands UF, it is now officially listed in the *Formulary*.

Although we currently cannot stock this product because of the shortage, Analatro® brand of black widow spider antivenin is currently available via an investigational protocol. Further, Merck will ship product for patients with symptomatic bites. Since black-widow-spider bites have a greater risk of being life threatening in children and the elderly, these patients will be given priority for the limited available product.

Sildenafil injection has a labeled indication for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening when patients are temporarily unable to take oral medications. This agent was approved for automatic IV to PO conversion.

IV sildenafil was added in the *Formulary* and restricted to short-term, off-label use in patients with congenital diaphragmatic hernias who have pulmonary hypertension and who are not fed prior to surgical repair of their hernia. It will be used as an alternative to inhaled nitric oxide or ECMO in these patients.

IV sildenafil is expensive. Overall, injectable sildenafil is 3 times more expensive than oral Revatio® and 14 times more than the compounded suspension from sildenafil tablets. The oral dose of sildenafil is twice the IV dose because it is 50% bioavailable.

On 8/30/2012, the FDA posted a safety warning about the use of sildenafil in children. FDA warned healthcare professionals that sildenafil should not be prescribed to children (ages 1 through 17) for pulmonary arterial hypertension (PAH). This recommendation is based on a recent long-term clinical pediatric trial showing that: (1) children taking a high dose of sildenafil had a higher risk of death than children taking a low dose did and (2) the low doses of sildenafil are not effective in improving exercise ability. Treatment of PAH in children with this drug is an off-label use (not approved by FDA)

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and a new warning, stating the use of sildenafil is not recommended in pediatric patients has been added to the Revatio® labeling. Healthcare professionals were reminded that use of this product, particularly chronic use, in children is an off-label use, not approved by FDA, and is not recommended. The Drug Safety Communication summarized data from a randomized, double-blind, placebo-controlled clinical trial of 234 patients with PAH, 1 to 17 years of age with mild to moderate symptoms at baseline. The P&T Committee determined these data were for long-term use and were not necessarily applicable for short-term use in diaphragmatic hernia repairs.

Sipuleucel-T is a biologic with a labeled indication for the treatment of asymptomatic or minimally symptomatic patients who present with metastatic castrate resistant (hormone refractory) prostate cancer. In June 2010, the P&T Committee designated it nonformulary and not available, but suggested that it should be available for “selected” patients in the outpatient setting. It has not been used because it could only be used in areas where the production plant is a direct flight connection to the location of use. A plant has recently been opened in Atlanta, Georgia.

A mainstay in the treatment of prostate cancer is hormone agonists that act to lower testosterone levels from the circulation, analogous to chemical castration. In some cases, patients can become refractory to this therapy and testosterone levels will rise despite the hormone treatment. Currently, chemotherapy is used commonly in patients who have become resistant to the hormone ablation.

Sipuleucel-T is the alternative to chemotherapy. An immunotherapy, sipuleucel-T activates the patients' own T-cells to attack prostate cancer cells. Therefore, the potency of this biologic is dependent on the patients' immune system. Its unique mechanism of action makes it personalized and unique for prostate cancer.

There are limited data regarding the use of sipuleucel-T. However, completed trials have shown an efficacy benefit in overall survival and survival rate when compared to placebo. Data have been inconclusive regarding the prolongation of disease progression. In addition, there have been results that indicate only mild to moderate adverse events. There are multiple trials in progress that aim to provide more information regarding its overall efficacy and safety profile. There are other therapies that could be used in these patients, and it is unclear how sipuleucel-T compares with these agents.

Patients must undergo 3 infusions of sipuleucel-T, each separated by at

least 2 weeks. Patients should be premedicated and monitored for acute infusion reactions. Common adverse events are chills, fatigue, fever, back pain, nausea, joint ache, and headache.

The cost of the 3 infusions can be high for the patient, but insurance company coverage may make it more affordable. In addition, the manufacturer provides a patient assistance program for eligible patients. The expected survival benefit is roughly 4 months.

Sipuleucel-T remains nonformulary and not available for inpatient use. It will be offered to outpatients who have tried and failed other chemotherapy options and who have been approved by their third party payer for coverage.

Recombinant topical thrombin was added in the *Formulary* and **bovine thrombin** was deleted and designated nonformulary and not available. For decades, topical bovine thrombin has been used as a hemostatic agent during operational procedures. Due to the concern of the associated antibody development with topical bovine thrombin, a plasma human thrombin and a recombinant human thrombin were developed. Whether recombinant human thrombin is just as effective and safe as topical bovine thrombin, and whether the anti-bovine thrombin antibody development is associated with clinical consequences were evaluated by the P&T Committee.

There have been several studies that compared the safety and efficacy of the different topical thrombins. There is no documented significant difference in efficacy between bovine thrombin and recombinant human thrombin. Though it has been purported that recombinant thrombin is safer (ie, less coagulopathy abnormalities), studies have failed to demonstrate statistical or clinical evidence to support these concerns. There may, however, be rare patients where bovine thrombin antibodies are relevant. Recombinant topical thrombin should be available for these patients. The choice of a topical thrombin for most patients will balance theoretical risks and economic considerations.

Based on current economics, however, there is little difference between the costs of these products. However, if the price difference between bovine and recombinant thrombin increases, the use of recombinant thrombin will be limited.

Zinc sulfate injection was temporarily added in the *Formulary*, since there is a shortage of **zinc chloride injection**. Zinc sulfate was recently discontinued; however, we will use our remaining supplies. Hopefully, the zinc chloride will be resolved by this time.

Injectable zinc is used to prevent zinc deficiency in patients receiving parenteral nutrition. Since the salt of zinc is irrelevant, a commercially available product will be used regardless of the salt.

Combivent® Respimat® inhalation spray was recently marketed for patients with chronic obstructive pulmonary disease on a regular aerosol

bronchodilator who continue to have evidence of bronchospasm and who continue to require a second bronchodilator.

Combivent® aerosol, the original formulation of ipratropium bromide and albuterol sulfate, will be phased out because it contains chlorofluorocarbons (CFCs). CFCs decrease the ozone layer. Combivent® inhalation aerosol is not supposed to be available after December 31, 2013. Supposedly, after January 1, 2014, Combivent® Respimat® spray will be the only form of ipratropium-albuterol inhaler.

Combivent® Respimat® (120-dose container) costs about 14% more than Combivent® (200-dose container). Until the CFC-containing product is no longer available, Shands UF will only stock Combivent®. One actuation of the Combivent® Respimat® spray is equal to two sprays Combivent®. The lower dose is possible because more Combivent® Respimat® reaches the lungs.

Combivent® Respimat® will be interchanged to Combivent® as long as both products remain on the market. Patients may use their own supply of Combivent® Respimat®, if ordered by the patient's prescriber as a patient's own medication.

Mirabegron is a beta₃-adrenergic agonist with a labeled indication for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. The starting dose of mirabegron ER is 25 mg per day; 50 mg per day is the maximum dose.

Effective May 2009, darifenacin, fesoterodine, flavoxate, solifenacin, and trospium, other drugs for overactive bladder symptoms, have been designated nonformulary and not available and are **interchanged to tolterodine ER**.

Mirabegron was designated nonformulary and not available and will be interchanged to tolterodine ER using the following interchanges: tolterodine ER 2 mg for mirabegron ER 25 mg and tolterodine ER 4 mg for mirabegron 50 mg. Patients may use their own supply of mirabegron ER, if ordered by the patient's prescriber as a patient's own medication.

Belviq® and **Qsymia®** are recently approved drugs for weight loss that were designated nonformulary and not available for use at Shands. Patients may use their own supply of Belviq®, but Qsymia® is a controlled substance and cannot be used while a patient is hospitalized.

Locaserin is a serotonin_{2c}-receptor agonist with a labeled indication as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of 30 or greater (obese) or 27 (overweight) in the presence of at least 1 weight-related comorbid condition (hypertension,

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dyslipidemia, and type 2 diabetes). One tablet is taken twice daily.

Warnings for locaserin include Serotonin Syndrome or Neuroleptic Malignant Syndrome-like reactions when used in combination with other serotonergic or antidopaminergic agents.

Qsymia® is a combination of **phentermine and extended-release topiramate**. Phentermine is a sympathetic amine with anorectic properties. As a single agent, phentermine has 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). Qsymia® has the same labeled indication as phentermine as a single agent.

Phentermine-containing products are controlled substances (CIV) and, thus, patients may not use their own supply from home. In 2011, the P&T Committee designated all dosage forms of phentermine nonformulary and not available.

Topiramate is an antiepileptic drug that also has been used for migraine prophylaxis. Weight loss has been a side effect of this agent. It is now used in this combination for this therapeutic weight loss effect.

Antihemophilic factor or factor VIII is used for the prevention and treatment of bleeding due to factor VIII deficiency or hemophilia A. Factor VIII acts in the coagulation cascade to accelerate the cleavage of factor X. Antihemophilic factors are also used for surgical prophylaxis in patients with hemophilia A.

After consultation with the Divisions of Adult and Pediatric Hematology and based on benchmarking with other similar academic medical centers, the *Patients Medications Brought into the Hospital and Self-Administration of Medications* policy will be modified to allow the inpatient use of injectable antihemophilic factors.

Helixate-FS® remains the factor VIII product listed in the *Formulary*.

Kogenate-FS® is the same product as Helixate-FS®. Patients are allowed to use their own supplies of **Advate®**, **Recombinate®**, or **Xyntha®**. Patients and their physicians may wish to use their own supply of antihemophilic factor to avoid the theoretical risk of antibody development to factors, but Shands will not acquire these nonformulary agents.

There currently is only one recombinant factor IX (Benefix®), which is listed in the *Formulary*. If additional products are marketed, this policy would also apply to nonformulary factor IX products.

Carfilzomib is a proteasome inhibitor with a labeled indication for the treatment of patients with

multiple myeloma who have received at least 2 prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. This drug is given intravenously over 2 to 10 minutes on 2 consecutive days each week for 3 weeks. Carfilzomib was added in the Chemotherapy Policy, but it remains nonformulary.

Doripenem has been the preferred carbapenem for most indications in adults. **Meropenem** has been the preferred carbapenem for pediatrics and central nervous system infections. However, new data suggest there are no clear clinical differences between these agents.

In January 2012, a Healthcare Professional Letter from Janssen was sent describing higher failure/mortality in patients receiving doripenem versus imipenem for the treatment of ventilator-associated pneumonia. The Anti-Infective Subcommittee identified several limitations to the study and the breadth of data (5 total trials), which did not necessarily support worse outcomes. But these mortality data will be considered when addressing appropriate dosing.

Recent cost data show that doripenem is almost 2 times more expensive than meropenem.

One reason doripenem was added in the *Formulary* was its improved activity against *Pseudomonas spp.* In particular, doripenem may be 1 dilution more potent than meropenem. A brief review of susceptibility patterns at Shands did not reveal a clear difference between these agents. Further isolate analysis may be warranted to see if there is a true difference.

Data from the TRUST database suggested about 20% of *Pseudomonas* isolates would remain susceptible to doripenem when meropenem or imipenem are resistant. These data are captured primarily from ward patients and about 30% of isolates are from ICUs. Therefore, it is unclear whether the data are generalizable based on preliminary data from our laboratory. When an organism is reported as resistant to imipenem (meropenem's and imipenem's susceptibilities match), the extended panel that tests for doripenem susceptibility will automatically be done.

Meropenem is now the preferred carbapenem for adult and pediatric patients in the management of multidrug-resistant (MDR) gram-negative bacilli. Doripenem is a second-line agent for the management of doripenem-susceptible, meropenem-resistant MDR gram-negative bacilli.

Influenza virus vaccines for the 2012-13 season have been released by FDA. These trivalent products contain an A/California/7/2009 (H1N1)-like virus, an A/Victoria/361/2011 (H3N2)-like virus, and a B/Wisconsin/1/2010-like virus. Shands is stocking Fluarix® for patients 3 years of age and older

and Fluzone® for patients 6 months of age to 3 years of age.

Nebivolol is a cardioselective beta-blocker that supposedly possesses vasodilatory properties due to nitric oxide modulation. However, the only labeled indication for nebivolol is hypertension, and it was approved based on its blood pressure lowering effects, not because of decreased adverse cardiovascular outcomes. It is used off-label for the treatment of heart failure, with some improvements shown in outcomes.

The FDA has sanctioned the manufacturer for inappropriately promoting the unique mechanism for this beta-blocker (ie, the vasodilatory and nitric oxide modulation) because these effects are unproven.

When nebivolol was reviewed in June 2008 as part of a review of all beta-blockers, it was designated nonformulary and not available. Patients could use their own supply from home and guidance was given for interchanging nebivolol to another beta-blocker depending on the use. Atenolol 50 mg daily or labetalol 200 mg twice a day could be used instead of nebivolol 5 mg daily for hypertension.

Metoprolol ER 25 mg, carvedilol 6.25 mg twice a day, or bisoprolol 2.5 mg daily could be used instead of nebivolol 2.5 mg daily for heart failure. However dosages of nebivolol as high as 40 mg have been used for the treatment of hypertension and doses as high as 10 mg for heart failure. Nebivolol is available as 2.5-, 5-, 10-, and 20-mg tablets. The P&T did not approve alternative dosing for higher dosages.

Because equivalent doses of formulary beta-blockers could not be established, nebivolol will no longer be therapeutically interchanged. It remains nonformulary and its use will be monitored.

Ondansetron injection is a 5-HT₃-receptor antagonist that has been used for chemotherapy-induced nausea and vomiting since 1991. Twenty years after its approval, the FDA issued a safety report recommending that single doses of ondansetron be limited 16 mg because of the risk of QT-interval prolongation and the risk of Torsades de Pointes.

The Medication Safety Subcommittee recommended that ondansetron be restricted to a maximum single dose of 16 mg (or 0.15 mg/kg in children) within a 4 hour period. The P&T Committee approved this dosage restriction.

Profilnine® SD is a 3-factor **prothrombin complex concentrate** (PCC) containing primarily factors II, IX, and X. PCC is also known as Factor IX Complex, but it is listed in EPIC as prothrombin complex concentrate in an attempt to prevent confusion with other factors (eg, recombinant Factor IX). Despite its labeled indication for the prevention and control of bleeding in patients with Factor IX deficiency due to hemophilia B, it is used primarily for

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the management of serious bleeding associated with excessive anticoagulation with warfarin.

When a 3-factor PCC is used to treat excessive anticoagulation, fresh frozen plasma (FFP) is usually given at the same time to supplement the amount of Factor VII (FVII). For life-threatening bleeding, guidelines from the American College of Chest Physicians (ACCP) recommend holding warfarin therapy and administering FFP, PCC, or recombinant FVIIa (NovoSeven® RT) along with 10 mg IV vitamin K, repeating if needed, depending on the INR.

PCC was added in the *Formulary* for use in life-threatening hemorrhages due to warfarin overdose. Each use is reviewed immediately after it is administered to assure appropriate use.

When PCC was added in the *Formulary*, it was not clear whether doses could be rounded like other antihemophilic products to the nearest vial size. This issue was clarified and doses may be rounded [up or down] 10% to achieve a reasonable dose. PCC will not be rounded to the nearest vial size like factor VIII and IX products.

Marqibo® is a once-weekly, intravenous liposomal dosage form of vincristine. It has a labeled indication for the treatment of adults with Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL)

in second or greater relapse or whose disease has progressed following 2 or more anti-leukemia therapies. This indication is based on overall response rate; improvement in overall survival has not been shown.

Serious adverse events such as low white blood cell counts with fever, low blood pressure, respiratory distress, and cardiac arrest occurred in 76% of the patients studied. The most common adverse effects observed during clinical studies include constipation, nausea, low blood cell counts, fever, nerve damage, fatigue, diarrhea, decreased appetite, and insomnia.

Prescribing information carries a black box warning alerting patients and health care professionals that the drug must be administered only through a vein (intravenously) because it is deadly if administered in other ways, such as into the spinal fluid. The boxed warning also states that Marqibo® has different dosage recommendations than vincristine sulfate injection alone. To avoid overdose, it is important for health care professionals to verify the drug name and the dose before administration. Special requirements for preparation of the drug are detailed in the label.

Liposomal vincristine was added in the Chemotherapy Policy and this issue was referred to the Medication Safety Subcommittee to establish appropriate safety measures to prevent confusion with regular vincristine. This product remains nonformulary.

Ziv-aflibercept is an intravenous angiogenesis inhibitor that inhibits the blood supply to tumors. It has a labeled indication in combination with FOLFIRI (folinic acid, fluorouracil, and irinotecan) to treat colorectal cancer in adults.

Ziv-aflibercept has a black-boxed warning alerting patients and health-care providers about the risk of severe and sometimes fatal bleeding, including gastrointestinal bleeding. Wound healing may also be impaired. The most common adverse effects observed in clinical trials include decreased white blood cell count, diarrhea, mouth ulcers, fatigue, high blood pressure, increased protein in the urine, weight loss, decreased appetite, abdominal pain, and headache.

Ziv-aflibercept was approved based on a study in patients with metastatic colorectal cancer who received oxaliplatin-based combination chemotherapy or whose cancer was removed by surgery but returned within 6 months after receiving oxaliplatin-based combination chemotherapy for adjuvant treatment. Ziv-aflibercept showed a modest improvement in overall survival (ie, 13.5 months versus 12 months) and an improvement of progression free survival (ie, 6.9 months versus 4.7 months). Ziv-aflibercept was added in the Chemotherapy Policy, but it remains nonformulary.

Oral Contraceptive Clots, from page 1

10,000 PYs in women using DRSP- or NGMN-containing products and between 0.9 to 14 events per 10,000 PYs in those using comparator OCs containing an older progesterone.³ Six of the trials found no significant difference in VTE risk between those using the newer versus the older OC formulations. Interestingly, 5 of these 6 studies were funded by the pharmaceutical company marketing the newer product. Essentially, the trials suggest a 0.9- to 3.3-fold increase in risk with the newer agents.³

The FDA concluded that the relative risk of VTE between the newer and older OC products is uncertain due to the inconsistencies in the literature.³ However, the absolute risk of VTE with OC use is extremely low, regardless of progestin-type, and considerably less than the incidence of VTE reported during pregnancy and post-partum (10 and 50 events per 10,000 PYs, respectively).⁴

Based on the evidence, the risks associated with the newer OC options appear to be minimal and all the concerning labeling should be interpreted in context. The 9 FDA-approved OCs containing DRSP, marketed under the names Beyaz®, Gianvi®, Loryna®, Ocella®, Safyral®, Syeda®, Yasmin®, Yaz®, and Zarah®, are all acceptable options

to prevent pregnancy. The products containing NGMN (Ortho Evra®) and ETON (NuvaRing®) provide a unique delivery system and more convenient dosing (once weekly and monthly, respectively). These products serve as practical alternatives for patients where adherence is an issue.

At Shands, only one OC is available in the *Formulary*, a generic version of norethindrone and EE combination product (Ortho-Novum®, Nortrel®). Before re-initiating therapy, the risk for VTE should be assessed, taking into consideration relevant acute and chronic diagnoses, surgical plans, ambulatory status, and concomitant therapies, as well as the drawbacks to discontinuing therapy. If the risks outweigh the benefits based on clinical judgment, plans to resume OC therapy should be deferred until discharge or earlier if indicated.

If treatment is postponed, specific directions for how to restart OC therapy should be provided, keeping in mind where the patient is in her monthly cycle, the number of doses missed, the type of OC used, any newly prescribed medications, and patient preference. The patient should be counseled to use a backup method (eg, condoms) until she has taken 7 consecutive doses. The duration of backup use may be extended if the patient is discharged

on a medication that compromises the efficacy of the OC (eg, rifampin, phenytoin, carbamazepine).

If OC therapy is continued during hospitalization, the current policy advises to either substitute using the formulary product or to ask the patient to use her own personal supply. For patients admitted due to a thrombotic event, an OC product containing an older generation progestin may be considered if OC therapy is warranted.

by Ji Lee, Pharm.D.

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PERSONALIZED MEDICINE PROGRAM

CYP2C19 Reporting Changes

The P&T Committee approved 2 changes to CYP2C19 genotype reporting. The CYP2C19 Decision Table will now interpret the *2/*17 genotype as an intermediate metabolizer phenotype. In addition, *10 allele will be reported for CYP2C19 but be considered "unknown or clinically uninterpretable."

A study that evaluated the isolated and interactive impact of common CYP2C19 genetic variants on the antiplatelet effect of chronic clopidogrel therapy, concluded that the *17 allele (gain-of-function) allele behaves like the *1 (wild type) allele in the presence of a *2 allele (loss-of-function). Another study examined the influence of CYP2C19*2 and *17 on on-treatment platelet reactivity and bleeding events in patients undergoing elective coronary stenting, the investigators concluded that the *2/*17 corresponded with a predicted phenotype of an intermediate metabolizer (*1/*2).

These studies suggest that *2/*17, which had been interpreted as "unknown" should be changed to the

same category as *1/*2, which is the "intermediate" metabolizer group. The same clinical therapy decision algorithm for *1/*2 (current intermediate group) now applies to *2/*17, *3/*17, *4/*17, *5/*17, *6/*17, and *8/*17 genotypes.

The validation procedures in the UF Pathology Laboratories for the CYP2C19 genotyping involved testing on 2 different genotyping platforms. Incidentally, 1 out of 20 test samples did not match. The mismatched samples were being called *10/*2 on GenMark and *2/*2 on QuantStudio. HapMap and pyro-sequencing confirmed the samples to be *10/*2. This led to further investigation, where it was recognized that *2 and *10 SNPs are adjacent on the chromosome, creating errors in the genotyping if a patient happens to carry both. As such, it was necessary to add the *10 allele to the Personalized Medicine Program custom chip in order to accurately call the *2 and *10 genotypes.

Since the *10 genotype will be generated in the laboratory, it was

agreed that the *10 allele should be reported in the medical record. The CYP2C19*10 allele is considered a loss-of-function allele that has been shown to decrease the metabolism of both S-mephenytoin and omeprazole. However, it is not "loss of function" based on absence of functional protein, and the various studies reviewed suggest there are substrate differences in the degree to which metabolism is decreased in the presence of the *10 allele.

Given the relatively limited literature on the *10 allele; and the absence of literature for clopidogrel, a clinical interpretation will not be provided for the *10 allele.

by Aniwaa Owusu Obeng, Pharm.D.