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B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met June 16, 2009. 3 drugs were added in the *Formulary* while one was deleted. 6 drugs were designated nonformulary and not available; 5 will be interchanged to formulary alternatives. Restriction criterion was changed for 1 drug.

◆ ADDED

Maraviroc
(Selzentry® by Pfizer)

Paricalcitol capsules
(Zemplar® by Abbott)

Raltegravir
(Isentress® by Merck)

◆ DELETED

Fenofibrate (Tricor® by Abbott)*

**Nonformulary and not available; interchanged*

◆ NONFORMULARY AND NOT AVAILABLE

Amlodipine, valsartan, HCTZ
(Exforge HCT® by Novartis)†

†Interchanged to components

Doxercalciferol
(Hectorol® by Genzyme)‡

‡Interchanged to paricalcitol

Fenofibrate
(multiple dosage strengths)§

§Interchanged to Fenofibrate, micronized 67 mg or 200 mg

Fenofibric acid
(Trilipix® by Abbott)¶

¶Interchanged to Fenofibrate, micronized 200 mg

Glucose chewable tablets
(generic)\\

\\May not use own supply

(continued on next page)

MEDICATION SAFETY

Proton pump inhibitors may reduce clopidogrel's effectiveness

The FDA has released an early communication regarding an ongoing safety review of the concomitant use of clopidogrel and proton pump inhibitors (PPIs).[1] Preliminary evidence suggests that the combination may make clopidogrel less effective and lead to an increased risk of major cardiac events such as cardiovascular death, stent thrombosis, recurrent acute coronary syndrome, and recurrent revascularization.[1-2] Since PPIs are commonly prescribed for GI prophylaxis in patients receiving anti-platelet therapy, the number of patients exposed to an increased risk may be substantial.

Until further guidance is provided by the FDA, providers should re-evaluate the need for starting or continuing treatment with a PPI in patients taking clopidogrel.

The proposed mechanism for the interaction involves competitive inhibition of the CYP2C19 isoenzyme. Certain PPIs have been shown to inhibit the conversion of clopidogrel to its active form. It is believed that the reduction in available active drug reduces the response to clopidogrel.

Several observational studies have focused on the clinical significance of the interaction. However, most of these analyses are available only as abstracts and cannot be thoroughly evaluated at this time.

In the Clopidogrel Medco Outcomes Study, researchers found that the risk of major adverse cardiac events was raised from 17.9% to 25.1% in patients also taking PPIs.[2] The overall risk of major adverse cardiovascular events was 51% higher, with a 70% increase in the risk of MI or unstable angina and a 48% increase in the risk of stroke or TIA.

In a study recently published in *JAMA*, use of clopidogrel plus PPI was associated with a 25% increased odds of death or rehospitalization for ACS compared with use of clopidogrel alone.[3] The rates of recurrent hospitalization for ACS and revascularization procedures were higher among patients taking clopidogrel plus PPI compared with those taking clopidogrel without PPI. However, the risk of death was similar between the two groups.

During the past calendar year, 1078 patients have received clopidogrel with a PPI at Shands at UF. These data suggest that this drug-drug interaction could be significant. Until further guidance is provided by the FDA, providers should re-evaluate the need for starting or continuing treatment with a PPI in patients taking clopidogrel. If acid suppression is warranted, H2 blockers (ie, ranitidine) or antacids are recommended alternatives.

By Candice T. Morris, PharmD

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3. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009; 301(9):937-944

INSIDE THIS ISSUE

Formulary update, *from page 1*

◆ INTERCHANGES

Fenofibrate, micronized for **Fenofibrate** (multiple dosage strengths)[**]

[**]See Table for details

Paricalcitol (Zemplar®) for **Doxercalciferol** (Hectorol®)[††]

[††]IV – increase dose by 77%; oral – mcg per mcg

◆ CRITERIA-FOR-USE CHANGES

Nilotinib (Tasigna® by Novartis)[‡‡]

[‡‡]Must be ordered using Chemotherapy Order Form

Thioridazine (Generics)§

§Restricted: Concomitant use with QT-prolonging agents prohibited

Ranolazine (Ranexa® by CV Therapeutics)¶

¶Concomitant use with moderate CYP 3A4 inhibitors or QT-prolonging agents no longer contraindicated

Maraviroc, in combination with other antiretroviral agents, has a labeled indication for treatment-experienced adult patients infected with CCR5-tropic human immunodeficiency virus type 1 (HIV-1), who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral regimens. Maraviroc has a novel mechanism of action; it is the first drug to inhibit viral entry into the cell through co-receptor CCR5 antagonism.

Because maraviroc's efficacy has been established only in patients with CCR5-tropic HIV-1, tropism testing (to determine the virus' specificity) is required for appropriate use. Maraviroc is not recommended for patients with dual/mixed or CXCR4-tropic HIV-1. The safety and efficacy of maraviroc have not been established in treatment-naïve or pediatric patients.

The recommended dose of maraviroc is 300 mg twice daily for most patients. If patients are concurrently taking a CYP3A-inhibitor (eg, fluconazole; ritonavir), the dose should be reduced to 150 mg twice daily. For patients concurrently taking a CYP3A-inducer (eg, rifampin), the dose recommendation is 600 mg twice daily. Patients should continue their optimized antiretroviral therapy based on genotype, phenotype, and previous exposure.

Overall, maraviroc is well tolerated. However, attention should be paid to the black-box warning regarding hepatotoxicity with allergic reaction features. Patients who present with signs or symptoms of hepatitis or a systemic allergic reaction (eg, pruritic rash; rise in IgE) with increased liver transaminases should be immediately evaluated for discontinuation of maraviroc.

Maraviroc is a novel antiretroviral agent and was added in the *Formulary* for the treatment of HIV/AIDS in treatment-experienced patients with CCR5-tropic HIV-1.

Paricalcitol capsules were added in the *Formulary* due to high volume nonformulary use. (Over the last year, 77 patients received paricalcitol capsules via the nonformulary process.) Paricalcitol has labeled indications for the prevention and treatment of secondary hyperparathyroidism in chronic kidney disease (CKD). Injectable paricalcitol is used in Stage 5 CKD and has been listed in the *Formulary* since August 1998. The oral capsule dosage form was originally evaluated by the P&T Committee in January 2006 for use in Stage 3 or 4 CKD but was not added in the *Formulary* at that time because of insufficient evidence.

Paricalcitol is a synthetic vitamin D analog that mimics the actions of calcitriol (ie, endogenous activated vitamin D). Activated vitamin D (and paricalcitol) reduces parathyroid hormone (PTH) levels in CKD. This prevents bone turnover and the consequences of calcium and phosphate resorption from bone. There are no data comparing oral paricalcitol with oral calcitriol or oral **doxercalciferol** (another synthetic vitamin D analog). There are published observational data for injectable paricalcitol in Stage 5 CKD associating its use with lower morbidity and hospitalizations compared with injectable calcitriol. Current opinion-based guidelines for Stages 3 and 4 CKD recommend therapy with an active oral vitamin D sterol (calcitriol or doxercalciferol) when serum levels of 25(OH)-vitamin D are greater than 30 ng/mL and plasma levels of intact PTH are above the target range.

Although paricalcitol is at least 12 times more expensive than calcitriol (which is available as a generic), it may result in more quality-adjusted life years (QUALYs) and life-years gained. Higher drug cost may be offset by reductions in other costs (but these assumptions are unproven). Recent data suggest that IV paricalcitol can be substituted for IV doxercalciferol by increasing the dose 77% and rounding to the nearest measurable dose (eg, 1.7 mcg paricalcitol IV for 1 mcg doxercalciferol IV, 3.5 mcg for 2 mcg, 5.2 mcg for 3 mcg). Based on differences in bioavailability, oral doses of paricalcitol and doxercalciferol can be interchanged on a mcg-per-mcg basis (ie, a 5 mcg dose of paricalcitol equals 5 mcg oral dose of doxercalciferol).

Because doxercalciferol (IV or oral) has not been used at Shands at UF in the past year and is not believed to provide any benefit over paricalcitol, it was designated nonformulary and not available and will be interchanged to an equivalent dose of paricalcitol (IV or oral).

Raltegravir, an antiretroviral for multi-drug resistant HIV, was added in the *Formulary*. Raltegravir was approved in 2007 and is the first integrase inhibitor available for clinical use. HIV-1 integrase is essential for viral replication; inhibitors of the integrase function demonstrate potent antiviral activity.

Raltegravir has a labeled indication for the treatment of HIV infection in combination with other antiretroviral agents in patients with persistent viremia despite ongoing antiretroviral therapies who are either treatment-experienced or have an HIV-1 strain resistant to multiple antiretrovirals. The initial dose of raltegravir is 400 mg twice daily to be administered either with or without food. If raltegravir is co-administered with rifampin, the dose is increased to 800 mg twice daily. Raltegravir is not indicated in the labeling for use in pregnant women, children less than 16 years, or adults greater than 65 years.

Two studies involving treatment-naïve patients and 2 studies involving treatment-experienced patients with multi-drug resistance demonstrate that raltegravir is effective in suppressing viral replication and maintaining immunologic integrity. The overall adverse event profile of raltegravir was similar to placebo in all these studies.

The most common adverse reactions of moderate to severe intensity are headache, nausea, asthenia, and fatigue. There are no contraindications associated with raltegravir.

The **fenofibrate** automatic interchange was updated to incorporate currently available products. The interchange, originally approved in 2003, previously did not match the products currently stocked (**Tricor**® 145 mg and 48 mg) or include newly available dosage strengths. There is a recently approved drug that is a metabolite of fenofibrate (**fenofibric acid**) which further complicated this issue.

Fenofibrate products are not bioequivalent by FDA standards (ie, regular vs. micronized products and various labeled strengths). In order to be AB-rated, products must be the same strength and dosage form. New fenofibrate products have been

(continued on next page)

RATIONAL THERAPEUTICS

Smoked! How to help patients who cannot smoke while hospitalized

Nicotine withdrawal symptoms, including irritability, craving, insomnia, headache, restlessness, anxiety, and poor concentration, are the result of abrupt discontinuation of nicotine intake. One study found that 89% of adult smokers admitted to a large, smoke-free, teaching hospital experienced at least 1 symptom of nicotine withdrawal within the first 48 hours of admission. Additionally, over half of the patients reported experiencing 3 symptoms of nicotine withdrawal (craving, restlessness, insomnia).[1]

(continued on next page)

Formulary update, *from page 2*
continually marketed with slight changes (in bioavailability or formulation) to the previous product in order to prevent interchanges in community pharmacies. This "product switching" is an attempt to prevent generic interchange for a product that generates a lot of revenue. In 2007, Tricor® was the #30 ranked brand name drug in terms of retail sales, accounting for over $1.1 billion in prescriptions. However, based on the amount of fenofibrate that is absorbed and reaches the systemic circulation, these products are equivalent and can be therapeutically interchanged.

The only fenofibrate study that documents any improved coronary outcomes with fenofibrate used a 200-mg micronized capsule available in Europe. The FIELD study compared fenofibrate to placebo in 9795 patients aged 50 to 75 years of age with type 2 diabetes not taking a statin at trial entry. Over the 5-year study period, fenofibrate use was significantly associated with a 21% reduction in coronary revascularizations and a 24% reduction in nonfatal myocardial infarction. However, this study failed to meet its primary endpoint of a significant decrease in coronary events.

In December 2008, fenofibric acid (**Trilipix®**) was approved by FDA as the newest fibrate. Fenofibric acid has a labeled indication to reduce triglycerides and increase HDL-C in patients with mixed dyslipidemia on optimal doses of a statin who have, or have risk factors for, coronary heart disease. It is the first fibrate approved by the FDA specifically for combined use with a statin. It is also approved as monotherapy for hypertriglyceridemia, hypercholesterolemia, and low HDL-C. Trilipix® appears to be yet another patent extension move since the patent for Tricor® will expire in 2011. The 135-mg delayed-release fenofibric acid capsule is equivalent to the 200-mg micronized capsule of fenofibrate.

Therefore, in order to limit the *Formulary*, only one fenofibrate product (ie, micronized fenofibrate) will be stocked in 2 dosage strengths (ie, 200 mg and 67 mg). Tricor®, Trilipix®, and all fenofibrate dosage strengths other than micronized fenofibrate 67-mg and 200-mg capsules were designated as nonformulary and not available and will be interchanged to the stocked products (see Table). In addition to decreasing inventory, this interchange has additional cost savings and safety advantages. The 200-mg capsule is available as a unit-dose package. This decreases workload prepackaging product, and prevents errors with prepackaging in the pharmacy. Also, the 200-mg capsule is 39% less expensive than Tricor®.

FENOFIBRATE AND FIBRIC ACID INTERCHANGES

DRUG DISPENSED	DRUG ORDERED
Fenofibrate 200 mg capsules (micronized)	Fenofibrate 160 mg tablets* Fenofibrate 150 mg capsules* Fenofibrate 145 mg (Tricor®) tablets* Fenofibrate 134 mg capsule Fenofibrate 130 mg capsule Fenofibrate 120 mg tablet* Fenofibric Acid (Trilipix®) 135 mg capsules
Fenofibrate 67 mg capsules (micronized)	Fenofibrate 54 mg tablets* Fenofibrate 50 mg capsules* Fenofibrate 50 mg tablets Fenofibrate 48 mg (Tricor®) tablets* Fenofibrate 40 mg tablets*

*Non-micronized

Exforge HCT® (amlodipine, valsartan, and hydrochlorothiazide) is a combination product with a labeled indication for the treatment of hypertension. It is not indicated for initial therapy. It is dosed once daily and may be used as add-on/switch therapy for patients not adequately controlled while receiving a combination of a calcium channel blocker, angiotensin receptor blocker, and/or diuretic.

The *Formulary* contains all of the corresponding dosage strengths of the individual components of Exforge HCT®. Therefore, Exforge HCT® was designated nonformulary and not available and will be automatically interchanged to its individual components.

Glucose chewable tablets are the second most dispensed nonformulary drug at Shands at UF. Currently, patients are allowed to use their own supply of glucose chews for the self-treatment of hypoglycemia. There was concern that the use of glucose chews while hospitalized may confound the results of routine glucose checks, leading to unwarranted adjustments in insulin regimens. (A rise in glucose due to self-treatment [without notifying the healthcare team] may be mistakenly perceived to be an indication for increased insulin requirements.) Therefore, glucose chewable tablets have been designated as nonformulary and not available. Patients will not be allowed to use their own supply. In adult patients receiving subcutaneous insulin, the approved standardized treatments for hypoglycemia are dextrose 50% and orange juice.

Nilotinib is a kinase inhibitor approved by the FDA in October 2007. It has a labeled indication for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to prior therapy that included imatinib. It is administered as an oral capsule twice daily. The agent has a black-box warning for QT prolongation and sudden deaths. Nilotinib was added in the *Chemotherapy Policy* (must be ordered using a *Chemotherapy Order Form*), but will remain nonformulary.

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Rational therapeutics, *from page 3*

The most obvious solution to prevent or treat nicotine withdrawal is nicotine replacement therapy (NRT). NRT is available in a variety of forms. The most commonly used, and only form currently available at Shands at UF (SUF), is the nicotine transdermal patch. Nicotine patches provide a continuous dose of nicotine throughout the day. This method of nicotine administration serves to diminish the symptoms of withdrawal associated with abrupt nicotine discontinuation without providing the peaks in nicotine serum concentration that are responsible for negative reinforcement. Nicotine patches are available at SUF in 3 doses: 7-, 14- and 21-mg/day. Patches should be applied to the torso and rotated daily. The starting dose for patients who smoke more than 10 cigarettes per day (half a pack) is 21 mg/day. Patients who smoke less than 10 cigarettes per day should be started on the 14-mg/day patch decreased to 7 mg/day after 4 weeks.[2] The most commonly observed adverse effect of the nicotine patch is erythema and pain at the site of the patch; however, the ability of nicotine to stimulate the sympathetic nervous system cannot be ignored, particularly in patients with underlying coronary artery disease or other forms of cardiac dysfunction. Additionally the backing of this transdermal patch system contains a metal component and, thus, should be removed if a patient is to undergo MRI. NRT is also available in the form of gum, lozenge, inhaler, and nasal spray. With the exception of the gum, these dosage forms all provide peaks in nicotine serum concentrations, albeit not as dramatic as those observed with cigarettes, and are more useful in the treatment of cravings. While NRT seems to be a straightforward way to address symptoms associated with nicotine withdrawal, it may not be the best option for all patients.

While NRT is generally considered no more harmful than smoking, it has not been evaluated for safety in all populations in which it is used. A retrospective case-control study found NRT to be independently associated with increased mortality (OR 24.6; 95% CI: 3.6-167.6).[3] The mechanism of this is unknown. One theory is that nicotine stimulates the cholinergic anti-inflammatory pathway, which attenuates the intrinsic immune response resulting in "immune paralysis." This may result in impaired clearance and overgrowth of bacteria in patients at high risk for infection, such as the critically ill.[4]

Alternatives to NRT for the temporary treatment of nicotine withdrawal are limited. Clonidine has long been used to treat the symptoms of opioid and alcohol withdrawal and is recommended as a second-line agent in the treatment of tobacco dependence. Clonidine is recommended as a second-line agent because of the danger associated with abrupt discontinuation of the medication and the variability in the dosing schemes that have been investigated. Oral clonidine doses range from 0.1-0.4 mg/day given in 2-3 divided doses. The dose-limiting adverse effects of clonidine are hypotension and sedation. Alternative pharmacologic therapies include bupropion, varenicline, and nortriptyline.[2] Given the amount of time necessary for these medications to reach full therapeutic efficacy, however, their use may not be appropriate for the temporary treatment of nicotine withdrawal symptoms. General symptom management and supportive care are best for the treatment of nicotine withdrawal in patients for whom NRT is not appropriate.

While pharmacologic agents may be useful in blunting the symptoms of nicotine withdrawal in patients while they are hospitalized, pharmacotherapy alone is not a substitute for behavioral modification therapy and post-discharge support in assisting patients to quit smoking permanently. These medications work best as adjunctive therapy. A number of programs are available to assist patients in smoking cessation after discharge through a variety of organizations including the National Cancer Institute (1-800-QUIT-NOW) and tobaccofreeflorida.com.

By Jennifer Bushwitz, PharmD
References available upon request to the Editor.