

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met March 18, 2008. 4 drugs were added in the *Formulary*, and 2 dosage forms were deleted. 4 products were designated nonformulary and not available; 4 criteria for use were changed; and, 5 interchanges were approved.

◆ ADDED

Darunavir
(Prezista® by Tibotec Therapeutics)

Floxuridine (Generic)*

*Restricted to chemotherapy prescribers and the Chemotherapy Order Form

Scopolamine Transdermal
(Transderm Scop® by ALZA Corporation)

Tipranavir
(Aptivus® by Boehringer Ingelheim Pharmaceuticals)

◆ DELETED

Procainamide Immediate-Release (Generic)†

Procainamide Extended-Release (Procanbid® by Monarch Pharmaceuticals)†

*Nonformulary and Not Available

◆ NONFORMULARY AND NOT AVAILABLE

Hepatitis B Immune Globulin (HepaGam B® by Apotex)†

*Nabi-HB® brand will continue to be used in the inpatient setting.

Oil of Wintergreen (Generic)

◆ CRITERIA-FOR-USE CHANGES

Cyclosporine Injection (Generic)§

*Standardized IV concentration 1 mg/mL [neonatal, pediatrics, & adult]

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POLICIES AND PROCEDURES

Heparin shortage: Interchange to enoxaparin?

The news has been full of reports about contaminated heparin from manufacturers who use Chinese suppliers of heparin raw materials. An intentionally added "contaminant" made from inexpensive animal cartilage (ie, an over-sulfated version of chondroitin sulfate, which has anticoagulant properties) has been associated with multiple reports of adverse effects and even fatalities.¹ These reports led at least 2 suppliers of heparin to recall their products. The recall resulted in a nationwide shortage of heparin products. During the shortage, hospitals receive only an allocated supply of heparin. At the time of the writing of this article, Shands at UF has been able to obtain adequate supplies of heparin.

However, during the shortage, the slightest glitch in the overall supply of unfractionated heparin (UFH) could result in the inability to adequately supply product for all the orders written at Shands at UF. In anticipation of this possibility, the P&T Commit-

tee approved a policy that allows the automatic interchange from UFH to enoxaparin as a "P&T Committee-Authorized Interchange." This policy was approved due to the need to quickly and efficiently move patients to an alternative drug regimen in the event of disruption in heparin supply. There are concerns that the increased workload could affect patient safety.

UFH orders for 5000 units every 8 to 12 hours would be converted to enoxaparin 40 mg every 24 hours or enoxaparin 30 mg every 24 hours when the patient's estimated creatinine clearance is less than 30 mL/min. Neurosurgery patients would receive UFH with any product that is reserved during the critical shortage and an automatic interchange would not occur. This proposal will be implemented only if needed.

REFERENCE

1. Public Health Advisory: Important Warnings and Instructions for Heparin Sodium Injection (Baxter). Created 2/11/08 and updated 2/28/08. Accessible online at: <http://www.fda.gov/cder/drug/advisory/heparin.htm>

MEDICATION SAFETY

Ketorolac + ibuprofen contraindicated

The concurrent use of ketorolac (Toradol®) and ibuprofen (Motrin®) is contraindicated according to the official package labeling. The concomitant use of these agents increases the risks of serious adverse events, such as adverse gastrointestinal effects or renal impairment.

Oral ketorolac is nonformulary and not available at Shands at UF. The only advantage of ketorolac is that it is available as an injection. Injectable ketorolac is limited to a maximum of 5 days' use because of the increased risk of gastrointestinal ulceration and nephrotoxicity with prolonged use. Orders may include both injectable ketorolac for use when a patient cannot take oral

medications and ibuprofen for when they can take medications orally. Since both ketorolac injection and ibuprofen are ordered, the risk of concomitant use exists.

Orders for oral and injectable nonsteroidal anti-inflammatory drugs (NSAIDs) must specify that these agents cannot be used at the same time.

INSIDE THIS ISSUE

- ◆ Removing allergy info

◆ **CRITERIA-FOR-USE CHANGES
(CONT.)**

Esmolol Injection (Generic)*

*Standardized IV concentration changed to 20 mg/mL [neonatal, pediatrics, & adult]; 10 mg/mL restricted to approval by a clinical pharmacist

**Fentanyl Transmucosal
(Actiq® by Cephalon)****

**Allowed in opioid-experienced patients without pulse oximetry

Nitroglycerin Injection††

††Additional standardized IV concentration (0.8 mg/mL) [adult list only]

◆ **INTERCHANGES**

**Lisinopril (Generic) for Fosinopril
(Generic)§§**

§§Interchanged to lisinopril (10 mg = 10 mg fosinopril)

**Lisinopril (Generic) for Moexepril
(Generic)¶¶**

¶¶Interchanged to lisinopril (10 mg = 7.5 mg moexepril)

**Lisinopril (Generic) for Perindopril
(Aceon® by Solvay)*****

***Interchanged to lisinopril (10 mg = 4 mg perindopril)

**Lisinopril (Generic) for Quinapril
(Generic)†††**

†††Interchanged to lisinopril (10 mg = 10 mg quinapril)

**Lisinopril (Generic) for
Trandolapril (Generic)†††**

†††Interchanged to lisinopril (10 mg = 2 mg trandolapril)

Darunavir is a protease inhibitor with a labeled indication for treatment-experienced adult patients with HIV-1 infections. Darunavir is boosted with concomitant ritonavir and taken with other antiretroviral drugs. Treatment-experienced patients are those patients infected with HIV-1 strains resistant to more than 1 protease inhibitor.

Darunavir, a high-priority nonformulary drug, was evaluated for possible addition in the *Formulary*. All non-formulary antiretroviral medications are considered high-priority drugs. Adherence to patients' outpatient regimens when they are admitted to the hospital is important as even a delay in therapy can contribute to HIV resistance and therapeutic failures.

Darunavir has shown superiority over comparator protease inhibitors in clinical trials evaluating efficacy in highly treatment-experienced patients. In contrast to other protease inhibi-

tors, darunavir is highly potent against wild-type and multidrug-resistant HIV-1 strains.

Darunavir has a safety profile similar to other protease inhibitors. The most common adverse effects reported in clinical trials associated with darunavir were nausea, vomiting, diarrhea, headache, and nasopharyngitis. The overall rate of discontinuation of therapy due to adverse events was 9% in patients receiving darunavir, while 5% of subjects in the comparator protease arm discontinued therapy due to adverse events. Recently, there has been an FDA warning about drug-induced hepatitis associated with darunavir-ritonavir use.

Darunavir was added in the *Formulary* for the treatment of HIV/AIDS in treatment-experienced patients who are admitted already taking darunavir. It is unlikely that this therapy would be started in the inpatient setting.

Tipranavir was also reviewed as a high-priority nonformulary drug. Tipranavir offers another treatment option for patients with an extensive history of previous antiretroviral therapy and who have resistance to other agents.

Tipranavir is a protease inhibitor with activity against HIV-1 strains resistant to multiple other protease inhibitors. It provides a treatment option as salvage therapy for patients with multidrug-resistant strains of HIV.

Tipranavir, boosted with ritonavir, has a labeled indication for combination antiretroviral treatment of HIV-1-infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors. Clinical studies indicate that tipranavir is an efficacious option for patients infected with multidrug-resistant HIV.

Adverse reactions most commonly associated with tipranavir are hypercholesterolemia, hypertriglyceridemia, diarrhea, and increased hepatic transaminases. The use of tipranavir is contraindicated in patients with moderate and severe (Child-Pugh B or C) hepatic disease. Clinical hepatitis and fatal hepatic decompensation have been reported in patients receiving tipranavir. Tipranavir has also been associated with fatal and nonfatal intracranial hemorrhage in patients with risk factors. Black box warnings have been added to the product information regarding the risks of hepatic decompensation and intracranial hemorrhage.

Tipranavir was added in the *Formulary* for the treatment of HIV/AIDS in treatment-experienced patients already admitted receiving this drug. Because of the safety concerns about hepatic decompensation and intracranial hemorrhage, tipranavir should be used as salvage therapy only and patients should be monitored closely.

Flouxuridine is an antimetabolite used

for the treatment of gastrointestinal adenocarcinoma that has metastasized to the liver. Flouxuridine has been administered intra-arterially in patients considered to be incurable with surgery; it was preferred to fluorouracil (5-FU) for intrahepatic administration because it is almost 100% metabolized through first-pass metabolism. Fluorouracil is only 20 to 50% metabolized through first-pass metabolism. Less systemic toxicity is expected with flouxuridine.

Flouxuridine is also given off-label by the intraperitoneal (IP) route for treatment of colorectal cancers and peritoneal metastasis. Administration of drug by the IP route allows large doses to be administered at the site of disease with less systemic toxicity.

Flouxuridine was shown to be effective for the treatment of patients with stage IV colorectal cancer with established peritoneal metastases when given IP after surgical debulking. This particular disease is very difficult to treat, with poor outcomes expected. Flouxuridine administered after surgical debulking has been shown to improve 5-year survival rates with minimal toxicity when compared with surgical debulking and systemic chemotherapy.

When flouxuridine is given IP, the most common adverse reactions are associated with the route of administration; the chemical peritonitis can be quite painful. There can also be technical complications associated with the IP port. Common adverse effects include nausea and vomiting.

Like all cytotoxic chemotherapy, flouxuridine is restricted to credentialed chemotherapy prescribers and can only be ordered using a Chemotherapy Order Form.

Transdermal scopolamine patches were evaluated for possible addition in the *Formulary* because of frequent nonformulary use. These patches have been used for the prevention of post-operative nausea and vomiting and for the treatment of excessive salivary secretions as part of end-of-life care.

Scopolamine is a belladonna alkaloid with anticholinergic properties. The transdermal system delivers 1 mg of scopolamine at a constant rate over 3 days. Following application behind the ear, plasma concentrations are detected within 4 hours with peak levels within 24 hours. The distribution of scopolamine is not well categorized, but it crosses the blood brain barrier (BBB).

Transdermal scopolamine has a labeled indication of post-operative nausea and vomiting (PONV); decreasing excessive secretion as part of end-of-life care is an off-label use. Excessive salivary secretions can lead to a noisy respiration, which is called "death rattle." Antimuscarinic drugs

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Formulary update, from page 2
are a common treatment for this condition based on their ability to dry secretions.

No clinical trials look specifically at the use of transdermal scopolamine for end-of-life care; however, 2 cross-over trials used the patch in patients with sialorrhea. These trials showed statistically significant decreases in drooling; however, all results were subjective.

Subcutaneous (SQ) scopolamine has been compared to other anticholinergics for end-of-life care. In these studies, about 60% of patients had benefits. No agent was found to be superior, although SQ scopolamine may have a faster onset of action compared to SQ glycopyrrolate. Additionally, scopolamine causes more sedation than glycopyrrolate (presumably because it crosses the BBB). This may or may not be desirable, depending on the patient's circumstances. Injectable glycopyrrolate is much less expensive than injectable scopolamine. Several palliative care textbooks and review articles recommend the use of scopolamine patches for excessive secretions, even though use is extrapolated from evidence using other routes of administration.

A systematic review and meta-analysis of randomized, placebo-controlled studies showed scopolamine patches to be superior to placebo (in terms of efficacy for the prevention of PONV). Only 17% of patients will not experience post-operative vomiting who would have on placebo. However, 18% will have visual disturbances, 8% dry mouth, 2% will experience dizziness, and 1% will be agitated. There are other agents in the *Formulary* that are more effective and less expensive (eg, ondansetron) for PONV. Based on the adverse effect profile of scopolamine, the delayed onset of action, and availability of cheaper effective alternatives, scopolamine patches are generally not recommended for use in preventing PONV. Because of the delayed onset, the patches are a poor choice for the treatment of acute nausea and vomiting.

Scopolamine patches may provide an administration and convenience advantage over a continuous SQ infusion or multiple injections of glycopyrrolate for maintenance therapy in end-of-life care. The antiemetic and sedative effects may also be useful. Based on the convenience of the patch and proven antisecretory effects of scopolamine for end-of-life care, the patch was added in the *Formulary*.

All oral procainamide products (**procainamide immediate-release** and **extended-release**) have been discontinued by their manufacturers for business reasons (ie, insufficient use to

support commercial viability). Immediate-release oral procainamide products were discontinued in 2006. Procanbid® was discontinued in November 2007. The low demand and availability of alternatives were cited as reasons for the discontinuation of these products. Oral procainamide products were labeled for the treatment of patients with life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia for whom the potential benefits outweigh the risks of serious hematologic adverse effects. Parenteral procainamide remains listed in the *Formulary*.

HepaGam B® brand of **hepatitis B immune globulin** was designated non-formulary and not available. **Nabi-HB®** brand of hepatitis B immune globulin remains listed in the *Formulary*.

HepaGam B® is the first hepatitis B immune globulin with a labeled indication for the prevention of hepatitis B recurrence following liver transplantation in HBsAg-positive liver transplant patients. Nabi-HB® has been used off-label for this use for many years.

Unfortunately, HepaGam B® contains maltose as a stabilizer. The glucose-measuring devices used in critical care units at Shands at UF measure maltose as glucose. The lack of specificity of our glucose meters makes the use of HepaGam B® inappropriate in the inpatient setting. The cross-reactivity of maltose and glucose would make tight glucose control in liver transplant patients extremely difficult. Therefore, until this issue is addressed, Nabi-HB® will continue to be used in the inpatient setting. The Liver Transplant Service will use HepaGam B® in the outpatient setting because only it will be reimbursed (ie, because it has the labeled indication for use).

Oil of wintergreen has been commonly used nonformulary as a room deodorizer. Oil of wintergreen, also known as methyl salicylate, can be quite toxic when ingested orally. It can cause salicylate toxicity and oral ingestion has been associated with fatalities. Thus, eliminating its use as a room deodorizer decreases the risk of it being inadvertently ingested.

Oil of wintergreen was designated nonformulary and not available. Alternate room deodorizers from central supply are recommended.

Standard intravenous (IV) concentrations for cyclosporine, esmolol, and nitroglycerin were either established or modified. Standardized IV concentrations are established to promote medication safety and make product delivery more convenient. There are separate standard IV concentration lists for neonates, pediatrics, and adults.

There has not been a standardized IV concentration listed for cyclosporine. Based on the most current practice patterns at Shands at UF, cyclosporine 1 mg/mL was added to the Adult, Neo-

natal, and Pediatric Standardized IV Concentration lists.

Esmolol 10-mg/mL IV bags were deleted from the adult and pediatric standardized intravenous concentration lists. Esmolol 20-mg/mL bags will now be used instead. The Neonatal, Pediatric, and Adult Standard IV Concentrations now list esmolol 20 mg/mL as the only standardized concentration. Esmolol ampules have been removed from the market, making it impossible to create a concentration greater than 20 mg/mL. The 10-mg/mL esmolol IV concentration will be allowed only in special circumstances and must be approved by a clinical pharmacist. The preparation of the more dilute 10-mg/mL bag requires dilution of the 20-mg/mL bag, which is quite complicated. Esmolol uses a special diluent, and a special procedure is required.

A more concentrated nitroglycerin standard concentration was added to the current 0.2 mg/mL and 0.4 mg/mL options; a 0.8 mg/mL option was added in the Adult Standard IV Concentration list. The more concentrated nitroglycerin solution will be useful for patients who require high doses of intravenous nitroglycerin.

The **criteria for oral transmucosal fentanyl**, or fentanyl "lollipops," were changed to allow "opioid-experienced" patients to be treated without a pulse oximeter monitor. When transmucosal fentanyl was originally added in the *Formulary*, it was specified that oxygen saturation monitoring was necessary for its use. At that time, it was specified that transmucosal fentanyl should be used only for burn patients undergoing short procedures when the patients do not have intravenous access.

The experience has been that oral transmucosal fentanyl use has been very safe in opioid-tolerant patients. However, there is still some concern regarding its use in opioid-naïve patients. The Medication Safety Committee endorsed a policy that would change the current restrictions on transmucosal fentanyl and liberalize its use in opioid-tolerant patients.

Transmucosal fentanyl remains restricted to burn patients who lack IV access, and it should be avoided in opioid-naïve patients. If transmucosal fentanyl must be used in a patient without opioid tolerance, the patient should have oxygen saturation monitoring initiated at the time of medication administration. Oxygen monitoring may be discontinued in patients who have been determined by a physician to be opioid-tolerant. Since there is no explicit definition for opioid-experience or opioid-naïve, the prescriber must note that the patient is

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MEDICATION SAFETY

Inappropriate patient allergy? Let's remove it.

Many patients report drug allergies that are not "true" allergies. A true drug allergy or hypersensitivity is an immunological response to a drug antigen resulting in symptoms such as skin rash, hives, angioedema, swelling, difficulty breathing, and/or anaphylaxis. Patients often unknowingly misclassify common adverse drug reactions or intolerances (eg, nausea or itching from opioids) as drug allergies.¹

Considering the common incidence of improper drug allergies in patients' medical records, it is important to have a consistent mechanism in place to remove them. A Shands core policy (CP 2.66) details the appropriate procedure for removing drug allergies. When a healthcare professional suspects an improper drug allergy, they should verify the allergy by speaking with the patient or family member and determine if the patient has tolerated the drug in the past. This information should then be relayed to the patient's physician. If the physician chooses to remove the allergy, an order indicating such must be written in the Physician Order section of the patient chart. The order should include the drug name and a

brief explanation of why the allergy is being removed (eg, patient reports only nausea after taking penicillin). A unit clerk will update the allergy information in the health information system (HIS) and a pharmacist will update the

information in the pharmacy's computer system after receiving the order.

REFERENCE

Pilzer JD, Burke TG, Mutnick AH. Drug allergy assessment at a university hospital and clinic. Am J Health Syst Pharm 1996;53:2970-5.

older and who are at risk for these complications, but who do not need an ACE inhibitor for heart failure, uncontrolled hypertension, diabetes, or renal disease.

Captopril, enalapril, and lisinopril were already listed in the *Formulary*. Benazepril, fosinopril, moexipril, perindopril, quinapril, and trandolapril were all designated nonformulary and not available. A dosage equivalency chart was developed, and pharmacists have reported that there has been no resistance to change to an equivalent dosage of lisinopril.

The automatic procedure eliminates the need to contact the prescriber each time an interchange is needed. The equivalent dosages are based on the following ratios: lisinopril 10 mg = benazepril or fosinopril or quinapril 10 mg = moexipril 7.5 mg = perindopril 4 mg = trandolapril 2 mg.