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B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met October 16, 2012. 1 drug was added in the *Formulary* and 1 was deleted and designated nonformulary and not available. Criteria for use restrictions were adopted for 4 drugs.

◆ ADDED

Elvitegravir, Cobicistat, Emtricitabine, & Tenofovir (Stribild®)

◆ DELETED

Nortriptyline Oral Solution (Generic)*

**Nonformulary and not available*

◆ CRITERIA FOR USE CHANGES

Albuterol Nebulized, Continuous (Generic)†

†Restricted to 5, 10, 15, and 20 mg/hr dosages

Bosutinib (Bosulf®)†

†Added in the Chemotherapy Policy

Dalfampridine (Ampyra®)†

†BPA if creatinine clearance is less than 50 mL/min

Stribild® is a once-a-day combination tablet with a labeled indication for the treatment of human immunodeficiency virus (HIV) infection in adults who have never been treated for HIV infection. Stribild® contains 2 new drugs (**elvitegravir** and **cobicistat**) and 2 previously marketed drugs that are listed in the *Formulary* (**emtricitabine** and **tenofovir**).

Elvitegravir is an HIV-integrase-strand-transfer inhibitor, which prevents HIV multiplication. Cobicistat is present in the combination to boost the effect of elvitegravir by inhibiting the enzyme that metabolizes elvitegravir (CYP3A4).

(continued on next page)

PROPOSAL

Delete codeine from the Formulary?

Codeine has been used in medicine for a very long time. It was approved by the FDA in 1939. It has been widely used for its pain-relieving abilities, often in combination with acetaminophen, or for its antitussive effects, usually in combination with guaifenesin.

The use of codeine has gradually decreased, and it is anticipated that the most recent warnings from the FDA will decrease its use further.[1] So, do we need codeine in the *Formulary* at Shands UF? The Medication Safety Subcommittee is requesting input from prescribers while more immediate restrictions are being proposed to promote patient safety.

"The metabolic conversion of codeine to morphine by CYP2D6 is what led to recent FDA warnings about its use."

Codeine is an opioid. It is a prodrug, which is converted to morphine to provide analgesia. Codeine alone does not provide pain relief. The metabolic conversion of codeine to morphine by CYP2D6 is what led to the FDA warnings. Some patients are "ultra-rapid" metabolizers of codeine and form more morphine than would normally be expected. Excessive morphine exposure in ultra-rapid metabolizers can cause respiratory depression and even death. This has occurred in children who receive acetaminophen with codeine for post tonsillectomy pain and in the children of breastfeeding women who are ultra-metabolizers.

The P&T Committee will be considering a proposal from the Medication Safety Subcommittee in November, which would remove codeine from all order sets. However, this article is intended to request responses for a further proposal to delete codeine and codeine-containing products from the *Formulary*, and designate codeine as not available for use at SUF.

Pediatric ENT decided to use other options for pain control in children post-tonsillectomy after the potential risks were discussed. Other services that have used codeine have made the same decision. Codeine, however, is a difficult drug to assess for complete removal from the *Formulary*. It is used, albeit infrequently, by several services and providers.

The pain services have already expressed support for this proposal. Not only are some patients at risk for excessive effects, but slow metabolizers do not achieve therapeutic goals with codeine. Other services have already switched to alternatives for pain (eg, nonsteroidal anti-inflammatory drugs and oxycodone). Dextromethorphan is listed in the *Formulary* as an alternative for suppressing a cough.

We are posting this proposal in the *Bulletin* to determine whether there are uses of codeine that justify its continued use, even if under some restrictions. Please send your comments to *hatton@shands.ufl.edu* by December 10, 2012.

REFERENCES

1. FDA drug safety communication: codeine use in certain children and/or adenoidectomy may lead to rare, but life-threatening adverse events or death. Accessed online October 12, 2012 at http://www.fda.gov/Drugs/DrugSafety/ucm313631.htm.

INSIDE THIS ISSUE

Formulary update, *from page 1*

Emtricitabine is nucleoside reverse transcriptase inhibitor (NRTI). It is marketed as Emtriva®. Emtricitabine has a black-box warning about its use in patients with HIV infection who are co-infected with hepatitis B.

Tenofovir is a nucleotide reverse transcriptase inhibitor that is marketed as Viread® as a single-ingredient. It is used in the treatment of HIV and hepatitis B infection.

Emtricitabine and tenofovir are available in combination as Truvada®, which recently received labeling for use in the pre-exposure prophylaxis of HIV infection in high-risk people. If used for this indication, patients have to be screened to make sure they are and remain HIV negative. Continued use of Truvada® in HIV-infected patients may lead to resistance.

Studies show that Stribild® is at least as effective as the 3-drug, once-a-day combination, Atripla® (efavirenz [Sustiva®], emtricitabine, and tenofovir) in maintaining undetectable amounts of HIV in patients. Atripla® was added in the *Formulary* in June 2010. (Stribild® contains elvitegravir and cobicistat instead of efavirenz.)

Stribild® is promoted as an effective combination that is taken once a day, which may improve adherence to a patient's treatment regimen. Adherence with an HIV-treatment regimen is important in the prevention of resistance. Stribild® will be expensive (around $30,000 per year), so use in treatment-naïve patients will need to be cost justified.

There may be some populations where Stribild® use will be considered (eg, pregnant patients, in whom treatment adherence may be an issue). Stribild® is listed as pregnancy Category B in its labeling, compared with Category D for Atripla®, because the efavirenz component has been shown to be teratogenic in monkeys. Stribild® is too new for guidelines to describe its appropriate role.

Stribild® was added in the *Formulary* to assure continuity of care for patients admitted on this combination agent. If patients are started on this drug as an inpatient, providers should determine if the patient will experience any issues with continuing therapy upon discharge (eg, insurance-coverage and copays).

Nortriptyline is a tricyclic antidepressant that inhibits norepinephrine and serotonin reuptake. It also has antihistaminic and anticholinergic effects. It has a labeled indication for depression in children age 6 and above and in adults. It has been on the market since 1964.

Nortriptyline has not been used much in children less than 12, and selective serotonin reuptake inhibitors (SSRIs) have minimized its use in older children and adolescents. It has been used in children for bedwetting and for attention deficit disorder (ADHD).

Nortriptyline oral solution is no longer commercially available. It was deleted from the *Formulary* and designated nonformulary and not available.

Nortriptyline oral solution has not been used recently at Shands UF, according to our computer records. Nortriptyline capsules remain listed in the *Formulary*, as do several other drugs for the treatment of depression.

Albuterol is a short-acting, beta-agonist that has long been used as a bronchodilator in patients with asthma and chronic obstructive pulmonary disease (COPD). There are some data on the use of continuous albuterol nebulization for status asthmaticus.

A small task force met to propose an improved method of ordering continuous albuterol nebulizations for adults and children. This group proposed that dosages be standardized to 5 mg/hr, 10 mg/hr, 15 mg/hr, or 20 mg/hr. Some orders for children are being done in mg/kg/hr using free-text doses, which can be problematic.

The Formulary Subcommittee recommended that EPIC be modified to allow only 5 mg/hr, 10 mg/hr, 15 mg/hr, or 20 mg/hr continuous albuterol nebulizations for both adults and children. These recommendations have been endorsed by the pediatric medical staff (including the Pediatric ED, PICU, and general Pediatrics). Adult doses are already standardized.

Although the 20 mg/hr dose is higher than the most recent National Institutes of Health guidelines for the treatment of an acute exacerbation of asthma, it was deemed reasonable. The NIH guidelines have not been updated since 2007, and there are some published studies using the 20-mg/hr dosage. The NIH guidelines recommend a maximum of 15 mg/hr for adults and 0.5 mg/kg/hour for children less than or equal to 12 years of age. The potential benefits of the 20 mg/hr dose for some treatment resistant patients may outweigh possible risks (eg, cardiovascular toxicity).

Bosutinib is an oral kinase inhibitor with a labeled indication for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy. It is given as a 500-mg once-a-day dose (5 tablets) with food. Doses may be escalated to 600 mg in patients who do not reach a complete hematologic response. The dose may be lowered for hematologic and nonhematologic toxicities.

Similar drugs include dasatinib [Sprycel®], imatinib [Gleevec®], and nilotinib [Tasigna®]. Imatinib was added in the *Formulary* in August 2001, and dasatinib was added in the *Formulary* in August 2006. Both are included in the Chemotherapy Policy. Nilotinib is not listed in the *Formulary*, but listed in the Chemotherapy Policy.

Bosutinib was evaluated in a single trial of 546 patients whose CML had progressed after failing imatinib or imatinib followed by dasatinib and/or nilotinib or who could not tolerate the effects of prior therapy. There was no comparison group. The results showed that 34% of the patients experienced a major cytogenetic response within 24 weeks. 51% of patients had a major response for at least 9 months.

The most common adverse effects associated with bosutinib use were diarrhea, nausea, thrombocytopenia, vomiting, abdominal pain, rash, anemia, fever, and fatigue.

Although bosutinib remains nonformulary, it was added in the Chemotherapy Policy requiring that it be ordered by credentialed providers using a Chemotherapy Order Form.

Dalfampridine is an oral potassium channel blocker with a labeled indication to improve walking in patients with multiple sclerosis. In January 2010, the Formulary Subcommittee voted to monitor the nonformulary use of this drug to determine whether it needs to be considered for possible addition in the *Formulary*. It has remained nonformulary, and in the last 6 months only one patient used their own supply of dalfampridine.

The FDA recently reported an increased risk of seizures when dalfampridine is used in patients who have decreased renal function. Dalfampridine is now contraindicated in patients with a CrCl of 50mL/min or less.

Despite low use, the Medication Safety Subcommittee recommended that a best practices alert (BPA) be built to alert prescribers and pharmacists if a patient is receiving dalfampridine and their CrCl is 50 mL/min or below. Since this drug is used rarely, an alert is important to minimize the risk of adverse effects.

NEWS

Compounding Pharmacies and Fungal Meningitis

It was not that many years ago that all drugs were compounded. Pharmacists made each prescription from a formula using mortar and pestles, volumetric flasks, and other measuring and mixing devices. Over time, most drugs were mass-produced by pharmaceutical companies in large plants into finished dosage forms. The Food and Drug Administration (FDA) regulates manufactured drugs, which are safe and viable for years, sometimes decades.

A famous error when making a liquid form of the antibiotic sulfanilamide led to the Food, Drug, and Cosmetic Act of 1938 that gives the FDA much of its regulatory authority over drug manufacturing. Sulfanilamide "elixir" made by the S.E. Massingill Company was responsible for the deaths of more than 100 patients in 15 states [1]. Diethylene glycol was used as the diluent for this liquid antibiotic. Diethylene glycol, commonly used in antifreeze, was a deadly poison. This led to regulations to assure that manufactured drugs are safe. It was not until 1962 that FDA laws were changed to require that drugs prove their efficacy.

In the 1980s, as chain pharmacies put economic pressures on independent pharmacies, compounding presented an opportunity for some pharmacists to fill a niche not filled by chains. Over the last 30 years, compounding of drugs has persisted and in some cases flourished. Organizations that advocate compounding, like the International Academy of Compounding Pharmacists and the Professional Compounding Centers of America, promote compounding as "personalized medicine" for patients who cannot use manufactured drugs or dosage forms.

Specific niches for compounded oral medications include making veterinary drugs, flavoring unpalatable medications for patients (especially children), making dosage forms for patients under hospice care who may not be able to take typical dosage forms, and concocting personalized hormone mixtures for both men and women. Topical ointments and creams have been a mainstay of compounding for decades. These oral and topical dosage forms have varying levels of acceptance by the scientific community, and critics point to the lack of scientific evidence to support their use and stability. Pharmaceutical chemists know that formulations affect the stability of the active ingredients. The risk of most compounded oral or topical drugs, however, is usually an under- or overdose.

There are situations when compounded oral products fill a specific niche. For example, the immunosuppressant tacrolimus is not available as an oral liquid. At Shands, we use a compounded oral suspension for children who have undergone transplantation. In this case, the benefits outweigh risks. Serum concentrations can be monitored to increase the chances for efficacy and limit the possibilities of toxicity. If there was a commercially available product, we would use it.

Compounding sterile products is more risky. There are stringent national guidelines that must be followed to minimize the risks of infectious complications. Sterile products from sterile ingredients are made all the time in our pharmacies. This is considered "low-risk" or "medium-risk" compounding depending on several factors. **Making sterile products from nonsterile ingredients is "high-risk"** compounding, and there are well-publicized cases of infections resulting from poorly prepared preparations.[2-4]

Since pharmaceutical manufacturers are inspected and regulated by the FDA, manufacturers are shut down when a quality problem is identified. This is one reason for the drug shortages. However, compounding pharmacies are regulated by state boards of pharmacy. Each state has its own rules and regulations and varying levels of enforcement.

One difference between compounding and manufacturing is scope. Compounding, when done appropriately, is for a specific patient. Compounding is not large-scale production. This presents logistical problems for the use of some compounded products in the inpatient setting. Since we only obtain compounded products for a specific patient, these drugs cannot be stocked or listed in our *Formulary*.

We rarely use sterile products made from nonsterile ingredients. We do not do high-risk compounding at Shands UF and obtain these products from a local compounding pharmacy. The benefit has to outweigh any risk. There cannot be a commercial product or lower-risk alternative.

Examples of "high-risk" products used at Shands UF include Modified Carnoy's Solution and glutaraldehyde. Modified Carnoy's Solution is used in the OR after removal of odontogenic keratocysts to decrease the recurrence of this condition.[5] Glutaraldehyde is used in the OR to toughen tissue allografts used in cardiac surgery and vessel repairs. There are published retrospective data suggesting that glutaraldehyde improves the durability of atrial and ventricular septal defect repairs.

Shands has a policy regarding the use of compounded products *(Specifications for Drug Procurement)*. Compounded products are only obtained from an outside vendor on an individual patient-specific basis. Proper written informed consent must be obtained from a patient prior to the administration of a sterile "high risk" product prepared from nonsterile ingredients and obtained from an outside pharmacy. The compounding pharmacy must meet the FDA's Compliance Policy Guide.[6] Chemicals used to produce these products must be pharmaceutical (USP/NF) grade and the final product must be checked by a reference laboratory for content, sterility, and pyrogenicity. The product must meet American Society of Health-System Pharmacists standards for compounded products.

The P&T Committee is reviewing Shands' policies in light of the tragedy associated with a compounding pharmacy in Massachusetts. Contaminated methylprednisolone acetate was received by 14,000 patients in 23 states, including Florida.[2] These injections were preservative-free ["personalized"] because they were being injected epidurally for back pain. Preservatives have been associated with adverse effects.

No patients at Shands or in Gainesville were administered contaminated methylprednisolone product. However, 2 clinics as close as Ocala administered these products to patients. The number of people infected from this contaminated product continues to rise and some people have died or have permanent disabilities. It may be months before we know the full extent of this tragedy because fungal meningitis has a slow onset and requires a prolonged treatment.[5]

A similar outbreak occurred 10 years ago.[7] That outbreak was attributed to contaminated raw materials. A contaminated production environment is most likely the culprit in the current outbreak. Further, the large scope of the problem is likely because the compounding pharmacy was acting more like a manufacturer, producing large amounts of product, and was not following good "manufacturing" processes. Sterility testing should have identified the problem before any product was distributed.

Current pharmacy compounding problems emphasize the importance of national standards. It explains why standards like the USP's Chapter 797 must be followed to minimize the risks of infectious complications from parenteral mixtures. Also, it re-enforces that commercial products should be used whenever possible, and a benefit-to-risk assessment should be done for any compounded product.

References available upon request from the Editor.

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