

# Drugs & Therapy

B • U • L • L • E • T • I • N

## FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met April 19, 2005. 2 drugs were added in the *Formulary* and 1 drug was deleted. 3 drugs were designated nonformulary and not available.

### ◆ ADDED

**Chlorothiazide Injection**  
(Sodium Diuril® by Merck)

**Sodium Phenylacetate-Sodium Benzoate**  
(Ammonul® by Ucylyd Pharma)

### ◆ DELETED

**Kaolin-Pectin**  
(Kaopectate® by Pfizer)

### ◆ NONFORMULARY AND NOT AVAILABLE

**Bismuth Subsalicylate**  
(Kaopectate®)\*

**Fibrin Sealant**  
(Crosseal® by Johnson & Johnson)

\*All Kaopectate® brand products are not available; bismuth subsalicylate [Pepto Bismol®] is listed in the *Formulary*.

**Palifermin**  
(Kepivance® by Amgen)

**Chlorothiazide injection** was reviewed because of increasing nonformulary use in patients with diuretic resistance. Oral chlorothiazide tablets have long been listed in the *Formulary*. Chlorothiazide injection was added as an additional dosage form.

Chlorothiazide is a thiazide diuretic that increases the excretion of water by inhibiting the reabsorption of sodium and chloride ions at the distal renal tubule. Thiazide  
(continued on next page)

## MEDICATION SAFETY

### OTC brand names can cause errors

**A**lthough there are hundreds of thousands of over-the-counter (OTC) drug products, there are only a couple hundred unique active ingredients. The pervasive marketing that prompts patients to choose a remedy often differentiates among OTC products.

Brand names mean something...or at least patients think they do. Tylenol® has become synonymous with acetaminophen. Patients may even think that brand name Tylenol® works better than generic acetaminophen.

Unfortunately, brand names do not always mean what we think they do, which can lead to medication errors. Products that change ingredients and "line-extensions" can mislead patients and their caregivers about what is actually being taken. Misunderstandings about what a patient is taking can create safety concerns.

In this month's *Formulary Update*, the confusion about what "Kaopectate" means is described. This is just an example of how a brand name has stayed constant, but the active ingredient has changed over time. In the Kaopectate example, patients may inadvertently be exposed to salicylate, which could result in allergic reactions, drug interactions, or even result in morbidity (Reye's syndrome). The patient or prescriber may not know that what they think is kaolin-pectin is actually bismuth subsalicylate. If a patient developed black stools on "Kaopectate," caregivers need to know that this is an expected adverse effect of bismuth. Not knowing what a patient is taking could cause unnecessary concern about a gastrointestinal bleed.

Line-extensions are OTC drug makers capitalizing on the recognition of a brand name. For example, there is a Kaopectate® Stool Softener that contains 240 mg of docusate calcium.

A close inspection of the packaging of this product reveals, "formerly Surfak." When a patient says they are taking "Kaopectate," are they taking an anti-diarrheal product or a stool softener? Additional probing may be necessary to determine what OTC ingredient the patient is taking. This could make a difference in a patient's treatment or even their diagnosis.

The Food and Drug Administration's (FDA's) OTC review process has inadvertently contributed to this problem. In the Kaopectate® example, the ingredient changes were forced when the FDA panel found the previous ingredients (first kaolin-pectin, and then attapulgitte) ineffective. "New and improved" on the label of an OTC drug may mean, "the ingredients of this product have been changed, but the brand name remains the same."

Marketing specialists have also contributed to the problem by trying to capitalize on brand name recognition. Large amounts are spent each year promoting OTC drugs. Using a recognizable brand name can increase sales by drawing consumers to a product among the vast number of choices in the OTC product aisle. A small percentage increase in sales equals hundreds of thousands of dollars.

In order to avoid medication errors, find out exactly what OTC products your patients are taking. Verify the ingredients of the specific product that they are taking. Unnecessary allergic reactions, drug interactions, or other complications may be avoided.

## ◆ INSIDE THIS ISSUE

- ◆ Vancomycin pre-approval required
- ◆ Prescribing methadone

**Formulary update, from page 1** diuretics in combination with loop diuretics are considered beneficial in patients who are resistant to loop diuretics alone. This combination has been particularly useful in patients with congestive heart failure.

Diuretic combinations should work on different segments of the nephron. Thiazides work on the distal tubule, and loop diuretics on the ascending loop of Henle. Targeting different areas of the renal tubule may help overcome and inhibit the excessive sodium chloride reabsorption that is thought to render loop diuretics alone ineffective in resistant patients.

Despite being on the market for decades, there is no generic form of chlorothiazide injection. Only brand name Sodium Diuril® is available. Each 50-mg vial costs less than \$9.

Like all thiazides, chlorothiazide can cause fluid and electrolyte imbalances. This is particularly important when chlorothiazide is used in combination with a loop diuretic like furosemide. All patients should be observed for evidence of electrolyte imbalances, particularly hyponatremia, hypochloremic alkalosis, and hypokalemia.

Intravenous chlorothiazide should be reserved for patients who cannot take oral medications.

**Sodium phenylacetate-sodium benzoate** injection was evaluated for addition in the *Formulary* because the investigational protocol that provided access to this product was closed. After evaluating the available evidence, Ammonul® was added in the *Formulary* for the management of patients with rare genetic disorders of urea metabolism.

Ammonul® has a labeled indication for adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle. In acute neonatal hyperammonemic coma, in moderate to severe episodes of hyperammonemic encephalopathy, and in episodes of hyperammonemia that fail to respond to an initial course of Ammonul® therapy, hemodialysis is the most rapid and effective technique for removing ammonia. In such cases, the concomitant use of Ammonul® can help prevent the re-accumulation of ammonia by increasing waste nitrogen excretion.

Sodium phenylacetate and sodium benzoate are metabolically active compounds that serve as alternatives to urea for the excretion of waste nitrogen. There are genetic disorders of urea cycle metabolism that result

in the accumulation of ammonia. Decreased activity of 6 different enzymes in the urea cycle can result in these metabolic disorders. The accumulation of ammonia results in serious medical complications, ranging from lethargy and poor feeding to delirium and coma. These crises are often precipitated by viral illnesses, high protein diets, stress, or trauma.

The combination of sodium phenylacetate and sodium benzoate was shown to be effective in improving survival in patients with acute hyperammonemic episodes in an observational study of 316 patients (1045 episodes) over 22 years. This orphan drug was approved for this indication based on these data. There is no other treatment option.

Each vial of Ammonul® costs approximately \$2200. Thus, therapy for patients, who require repeated treatments, can be extremely expensive.

An important medication safety issue with this product is the route of administration. If Ammonul® extravasates, it can cause tissue necrosis. Therefore, it must be administered via a central line.

**Kaolin-pectin** was deleted from the *Formulary* because it has not been on the market for quite some time. **Kaopectate®**, a brand name often considered synonymous with the mixture of kaolin and pectin, was also designated nonformulary and not available. This was done because of the potential for confusion regarding Kaopectate® and its formulation changes and multiple products under the same brand name.

Kaolin and pectin were removed from the market when an FDA review panel for over-the-counter (OTC) products determined that there was insufficient evidence for its effectiveness. Kaopectate® was then reformulated to attapulgit. Attapulgit is a clay-like powder that was thought to work by adsorbing the bacteria or virus causing diarrhea. The final rule of the FDA OTC review panel also found that attapulgit had insufficient evidence of effectiveness.

Kaopectate® now contains bismuth subsalicylate, which is confusing. Bismuth subsalicylate and loperamide are the only ingredients still marketed as OTC antidiarrheal products. Most prescribers are unaware of these changes.

Bismuth subsalicylate is already listed in the *Formulary*. Since there is no kaolin-pectin mixture on the market, listing "Kaopectate®" is unnecessary. Also, prescribers who order Kaopectate® may not appreciate that they could be getting a product that contains a salicylate.

Bismuth subsalicylate products should not be used in children with chicken pox or flu symptoms because of the association with the develop-

ment of Reye's syndrome. They also should not be used in patients with a salicylate hypersensitivity. There also may be drug interactions with salicylates not expected with kaolin and pectin. Therefore, prescribers will be contacted for an order clarification if they order "Kaopectate."

Crosseal® brand of **fibrin sealant** was evaluated as a possible addition in the *Formulary*, but was determined to offer no advantage over Tisseel®, the fibrin sealant that remains in the *Formulary*. Crosseal® was not added and was designated nonformulary and not available.

Crosseal®, like Tisseel®, is a 2-component fibrin sealant. The main ingredient in the first component syringe is human fibrinogen; tranexamic acid is included to prevent degradation of fibrin. The main ingredients of the second component syringe are human thrombin and calcium chloride. Thrombin transforms fibrinogen into fibrin and forms a "clot." The component solutions are mixed in a common joining piece at the end of the 2 syringes, and it applied at the wound site like epoxy glue.

Crosseal® has a labeled indication as an adjunct to hemostasis in patients undergoing liver surgery, when control of bleeding by conventional surgical techniques, including suture, ligature, and cautery, is ineffective or impractical. Fibrin sealants have been used off-label in a variety of surgical procedures. They have been used for hemostasis, tissue adhesion, and for the local delivery of exogenous substances that have been mixed with the sealant.

The FDA assesses efficacy of fibrin sealants by using time to hemostasis. The clinical study highlighted in Crosseal®'s labeling is the only published controlled trial for this specific fibrin sealant. The results suggest a shorter time to hemostasis, but blood use was similar to standard topical hemostatics.

Since fibrin sealants are plasma-derived products, there is a risk of viral contamination. Viral inactivation/depletion methods minimize this risk, however.

Crosseal®'s label has a black-box warning stating "Crosseal® must not be used in contact with CSF or dural matter." This warning comes from reports in other countries of fatal reactions associated with the use of Crosseal® in neurosurgical procedures. Therefore, Crosseal® could not have replaced Tisseel® in the *Formulary*; it could only have been added in the *Formulary* as an alternative.

(continued on next page)

### Formulary update, from page 2

Crosseal® is at least 12% more expensive than Tisseel® per vial. Both products are needleless systems. Further, having Crosseal® could result in inadvertent use in neurosurgeries, which is explicitly contraindicated by the Crosseal® labeling.

**Palifermin** is a recombinant form of keratinocyte growth factor (KGF), which stimulates the growth of cells in the skin and on the surface layer of the mouth, stomach, and colon. Its labeled indication is to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support. It was reviewed proactively because of potential for use at Shands at UF. It is very expensive, so appropriate use will be a major concern.

The published data for palifermin are limited. There is 1 randomized, controlled trial that showed impressive results for palifermin in patients undergoing autologous hematopoietic stem cell transplantation (HSCT). Palifermin was given 3 days before total body irradiation (TBI) and 3 days afterwards. The conditioning regimen was very aggressive and included

TBI and large doses of etoposide and cyclophosphamide.

Mucositis was assessed using ordinal scales and was significantly less in the palifermin group compared with controls. Palifermin showed impressive results in secondary outcome variables, including less use of narcotics, lower incidence of febrile neutropenia, lower use of total parenteral nutrition, and a trend towards fewer blood-borne infections.

However, these data do not have external validity at Shands at UF. The Bone Marrow Service does not use the same conditioning regimen for autologous HSCT as used in the published study. The Shands regimen is less aggressive. Further, most of our transplants are allogeneic transplants that use methotrexate as part of the regimen for the prevention of graft-versus-host disease. Since palifermin should not be administered within 24 hours of myelotoxic chemotherapy, it is unclear how it should be used in this population.

Common toxicities associated with palifermin include skin rashes, erythema, and pruritus and are linked to its effects on epithelial tissues. Oral disorders including dysesthesia, tongue discoloration, tongue thickening, and taste changes have been reported. As

with any protein, there is potential for immunogenicity. The clinical significance of antibodies to palifermin is not known at this time. Palifermin should not be used in non-hematologic malignancies because of concerns about stimulating tumor growth.

Other logistical issues with palifermin exist. Administering palifermin 3 days before transplant would either increase bed utilization or stress clinic resources in the Bone Marrow Transplant Clinic (eg, require weekend clinic hours). Since it is expensive (ie, \$8000 for a 6-day course), palifermin would significantly add to pharmaceutical expenditures. Whether there would be offsetting cost savings (eg, shorter lengths of stay, less infection) in the Shands at UF patient population is not known. The Bone Marrow Service is currently assessing their incidence of mucositis to better assess the potential for this agent.

These concerns, along with the limited data that are applicable to patients at Shands at UF, led to the conclusion that there is insufficient data to recommend the addition of palifermin at this time. As additional data become available, palifermin will be re-assessed. In the interim, it will not be available.

## ANTI-INFECTIVE STEWARDSHIP

# Vancomycin pre-approval required after May 2nd

**O**n May 2, 2005, a 6-month pilot began that requires pre-approval of intravenous vancomycin before it can be prescribed for empiric or therapeutic use. Vancomycin use for surgical prophylaxis will not require pre-approval. The goal of this pilot is to decrease inappropriate vancomycin use and decrease the risk of antibiotic resistance, especially vancomycin-resistant enterococcus (VRE).

Despite a year of interventions by the Successful Antimicrobial Management (SAM) Program (previously known as the Anti-Infective Stewardship), vancomycin use continues to be high. The prevalence of VRE continues to increase. The success of the 6-month pre-approval pilot will be measured by compliance with the Centers for Disease Control (CDC) guidelines for vancomycin use. The P&T Committee will review the results of this pilot in January 2006.

Prior to ordering intravenous vancomycin for empiric or therapeutic uses, the prescribing service will have to receive approval from either the SAM or the Infectious Diseases Consult Service. The number for the SAM is 258-5944. This service is available between 7 am and 11 pm daily. Van-

comycin orders approved for empiric therapy that do not meet CDC criteria for continued use at 96 hours will be discontinued unless a call is made to the SAM service providing the rationale for continuation.

The SAM has been meeting with many of the medical services that frequently prescribe vancomycin over the last several weeks to explain the rationale for this program. By promoting the appropriate use of vancomycin, the goal is for there to be few SAM interventions. "Appropriate" use of vancomycin will be determined by the CDC criteria, which have been endorsed by the Shands at UF P&T Committee. Guidelines summarized in the following lists should aid the prescriber in determining what is an appropriate use for vancomycin.

### Vancomycin is appropriate for:

- Serious infections caused by beta-lactam resistant gram-positive organisms (eg, Methicillin-resistant *S. aureus* [MRSA] or *S. epidermidis*, and ampicillin-resistant enterococci).
- Infections caused by gram-positive organisms in patients who have serious allergies (eg, anaphylaxis, laryngeal edema, or urticaria) to beta-lactam antimicrobials.

- Empiric initial therapy for meningitis until gram-stain or culture results are available.

### Vancomycin is not appropriate for:

- Treatment after a single blood culture for coagulase-negative staphylococcus, if other blood cultures taken during the same time frame are negative.
- Eradication of MRSA colonization.
- Continued empiric use (greater than 72 hours) for presumed infection in a patient whose cultures are negative for beta-lactam resistant gram-positive organisms.
- Febrile neutropenia, unless evidence indicates that a patient has an infection caused by a gram-positive organism.

The process used for vancomycin pre-approval will also apply to imipenem. Imipenem is indicated for multiple-drug-resistant isolates, necrotizing pancreatitis, and failure of primary therapy.

The ultimate goal of the SAM is to stabilize or decrease the development of antibiotic resistance through improved use of antibiotics. Prudent use of antibiotics is only part of the solution to this problem. Good infection control procedures, especially hand washing, are also important in decreasing the incidence of difficult-to-treat infections.

This publication is produced by the Drug Information and Pharmacy Resource Center under the direction of the Department of Pharmacy Services and the Pharmacy and Therapeutics Committee.

**EDITOR,  
DRUGS & THERAPY BULLETIN**

Randy C. Hatton, PharmD

**DIRECTOR,  
PHARMACY SERVICES**

Alan Knudsen, MS, RPh

**CHAIRMAN,  
PHARMACY & THERAPEUTICS  
COMMITTEE**

Ricardo Gonzalez-Rothi, MD

**EDITING, DESIGN, & PRODUCTION**

Shands HealthCare's Publication Svcs.

© Copyright 2005. All rights reserved.

No portion of the *Drugs & Therapy Bulletin* may be reproduced without the written consent of its editor.

**FOR MORE INFORMATION,  
VISIT US ONLINE**

<http://shands.org/professional/drugs/bulletin.htm>

**SHANDS**

Shands at the University of Florida

**DRUG INFORMATION SERVICE**

PO Box 100316

Gainesville, FL 32610-0316

NON-PROFIT ORG.  
U.S. POSTAGE  
PAID  
GAINESVILLE, FL  
PERMIT NO. 94

**DRUG INFORMATION FORUM**

## When can I prescribe methadone?

**T**he Drug Information and Pharmacy Resource Center frequently receives questions about the limitations on the use of methadone. Methadone is a potent synthetic opioid unrelated to morphine that is most often associated with narcotic (ie, opioid) detoxification and maintenance treatment of narcotic addiction.

Methadone is used for the treatment of acute and chronic pain, although dosing can be difficult, which may discourage its use. Methadone has a long and unpredictable half-life, and the dosage may need to be adjusted after repeated dosing. At the onset of therapy, methadone's duration of effect is 6 to 8 hours, and frequent dosing may be needed. After about 2 or 3 days, the dosing interval needs to be lengthened to every 12 or 24 hours to avoid adverse effects of methadone accumulation (eg, respiratory depression).

There are no legal restrictions on the use of methadone for acute or chronic pain. There are legal limitations, however, on the use of methadone for opioid detoxification and addiction. These restrictions have contributed to the under use of methadone for pain.

Under federal law, methadone may be prescribed for maintenance therapy

of addiction in ambulatory patients only by physicians who have a special license to prescribe opioid therapy for addiction and who are affiliated with a licensed opioid treatment program. Thus, the typical physician will not be prescribing methadone for opioid detoxification or opioid addiction maintenance.

---

**Methadone is a potent synthetic opioid... associated with narcotic detoxification and maintenance treatment of narcotic addiction.**

---

But what happens when a patient receiving methadone for opioid addiction is separated from their treatment facility and needs emergency treatment? A practitioner who is not part of a narcotic treatment program may administer narcotic substances to an addicted individual to relieve that individual's acute withdrawal symptoms while the practitioner arranges to refer the individual to a narcotic treatment program. Not more than 1

day's medication may be administered at a time. This treatment cannot last for more than 3 days and may not be renewed or extended.

What happens when a patient receiving methadone treatment of opioid addiction is admitted to the hospital? If a patient is admitted for an acute medical illness or for a surgical procedure, any treating physician may and should prescribe the patient's maintenance methadone while the patient is hospitalized. It is important that maintenance methadone be continued during hospitalization in order to avoid withdrawal and potential complications in medical, surgical, and pain treatment. Thus, any physician with a standard, unrestricted Drug Enforcement Administration (DEA) license may prescribe maintenance methadone to a patient who is hospitalized for a cause unrelated to addiction.

There are no restrictions on the use of methadone for the treatment of pain, other than the typical restrictions of other Schedule II controlled substances. Methadone may be prescribed for opioid dependence outside of a methadone treatment program only in specific situations.