FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met May 16, 2006. 2 drugs were added in the Formulary and 2 drugs were deleted. The age-of-use criterion for 1 drug was modified.

◆ ADDED

Cetuximab* (Erbitux® by Bristol-Myers Squibb)
Cholestyramine Light in Aquaphor® (compounded)
*Restricted to credentialed chemotherapy prescribers

◆ DELETED

Amyl nitrate (generic)
Doxacurium
(Nuromax® by Abbott)

◆ CRITERIA FOR USE

Promethazine (Phenergan® & generics)*
*Cannot be used in children less than 2 years of age

Cetuximab is a recombinant, human-mouse chimeric monoclonal antibody that binds to epidermal growth factor receptors (EGFR). Overexpression of EGFR on cancer cells has been associated with a poor prognosis, decreased survival, and a higher incidence of metastasis. Cetuximab currently has labeled indications for the treatment of metastatic colorectal cancer intolerant to irinotecan-based chemotherapy and in combination with radiation therapy for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) or as a single agent for the treatment of recurrent or metastatic SCCHN in patients who have failed platinum-based therapy. It was evaluated for addition in the Formulary because it is an injectable oncology (continued on next page)

NEWS

Prescribing generics improves compliance

A recent study published in the Archives of Internal Medicine suggests that compliance (adherence) is 60% better for generics than nonpreferred brand name drugs.1 In this study, which was done in relatively young patients with a third-party prescription drug program and a 3-tiered formulary, compliance was best with generic drugs, less with brand-preferred drugs, and worst with nonpreferred brand name drugs. These compliance estimates were based on refill data and may actually underestimate the difference in compliance between inexpensive generics and more expensive brand name drugs. If a patient refused to fill the initial prescription because of cost, then it would not have been included in this study’s estimate of compliance.

Tiered formularies are designed to steer patients towards prescriptions that are less expensive for the employer or other agency that provides the prescription benefit. With 3-tiered formularies, a patient’s co-pay or “out-of-pocket” expenditures increases with each tier. Generic co-pays are always the least expensive. Preferred brands are often chosen because manufacturers provide rebates to third-party payors. Nonpreferred brands are more expensive or are not deemed medically necessary in the benefit plan (eg, lifestyle drugs). This study did not state the co-payments that patients were required to pay for each tier and did not give examples of the types of drugs in the third tier. Although not proven in this study, the implications are that patients’ compliance rates increase when they have to pay less “out of pocket” even when they have a prescription drug benefit.

In this study, the compliance rate was lowest for inhaled corticosteroids (ie, 20.6%). The importance of compliance for the treatment of asthma is well known for the prevention of acute exacerbations, which can be extremely serious and require hospitalization. The study also showed that older patients and patients with higher incomes were more compliant. The estimate of 60% greater compliance with generic drugs was adjusted for drug class and age.

Unfortunately, most prescribers do not know what the preferred brands are in a patient’s prescription drug plan.2 Therefore, it is always a good option to choose a generic when there are equally effective agents in a therapeutic category. A list of selected generic choices within some therapeutic categories can be found on our intranet site at http://intranet.shands.org/pharm/Drugs%20Available%20As%20Generic.pdf.

It is recommended that prescribers ask patients if they have difficulty paying for their prescriptions and to determine if there are less expensive alternatives when needed.3,4 Pharmacists can help prescribers determine what options exist in a patient’s prescription benefit plan.

With the establishment of Medicare Part D, there are now many more patients who have a prescription benefit plan. It is difficult to keep up with the preferred drugs in each plan. Thus, the use of generics is a good option when there is a generic alternative within a category. Lack of patient response to drug therapy may be a reflection of their lack of compliance because of their inability to pay for their prescriptions.4

References available upon request to the editor.

INSIDE THIS ISSUE

◆ Early warfarin therapy
◆ Patients’ own meds
◆ Dietary supplements
Cetuximab was added for use for its labeled indications when patients cannot tolerate treatment in the outpatient setting and when patients are admitted for another medical problem and their cetuximab treatment is due.

**Cholestryamine** is a resin that binds bile acids. When given orally, the binding of bile acids in the intestine indirectly decreases serum cholesterol. Cholesterol is a precursor for bile acids. Cholestyramine stimulates cholesterol synthesis to replace the bile acids eliminated in the feces, but shunts cholesterol into the bile acid synthesis pathway. This causes the liver to increase cholesterol uptake and decreases serum cholesterol. Cholestyramine Light is sugar-free (eg, contains aspartame), while regular cholestyramine contains sucrose.

**Aquaphor®** (white petrolatum) is used alone as a topical protectant. Pharmacists use Aquaphor® to compound many topical products because it easily forms emulsions with aqueous solutions and oily substances.

**Cholestyramine Light in Aquaphor®** has been a commonly requested nonformulary mixture for use as a “butt paste” in patients with treatment-resistant diaper dermatitis. It was evaluated because of its high volume of use.

Good hygiene (eg, prompt removal of stool and urine), cleansing with warm water and a mild soap, and completely drying the area (eg, before re-applying a diaper) are very important in the treatment of diaper dermatitis. Zinc oxide is the most commonly used protectant.

In reviewing the evidence regarding the mixture of Cholestyramine Light in Aquaphor®, no randomized trials documenting efficacy were found. There are, however, case reports supporting this mixture. 2 case series showed resolution of refractory skin irritation in patients with ostomies who failed traditional therapies. There is also 1 published case report of resolution of diaper dermatitis in a patient who was refractory to all other therapies. The Dermatology Division supports the use of this product for resistant diaper dermatitis and supports its addition in the *Formulary*. Also, several pediatric practitioners support its addition. The rationale for this mixture is that topical cholestyramine binds bile acids that are irritating to the skin.

Therefore, the P&T Committee added compounded Cholestyramine Light in Aquaphor® in the *Formulary*. Orders written for “Butt Paste” will not be honored and will require a clarification (ie, orders must be for “Cholestyramine Light in Aquaphor®”).
**COST-EFFECTIVE DRUG THERAPY**

**Starting warfarin therapy early shortens LOS**

There is a bed shortage within our institution causing patients to wait to receive care. As healthcare professionals, we are currently seeking innovative ways to increase bed availability. A way to “add beds” is to efficiently treat patients, thereby minimizing length of stay (LOS). Early initiation of oral anticoagulants is an efficient method of treating deep venous thrombosis (DVT) and pulmonary embolism (PE). By starting patients’ anticoagulation early, they will stabilize sooner, which could allow earlier discharge and increase available beds.

The most recent guidelines for the treatment of venous thrombosis recommend concomitant administration of heparin and warfarin at the time of diagnosis of DVT or PE (ie, both drugs started on day 1). In addition, day 1 initiation of warfarin is recommended for patients with a known protein C deficiency or other thrombophilic states.

Despite the guideline’s recommendation for simultaneous oral anticoagulation at time of DVT/PE diagnosis, there may be a problem with day 1 warfarin treatment. The main controversy surrounding same-day initiation of warfarin and heparin is the theoretical risk of creating a period where the patient is hypercoagulable.

The risk of a hypercoagulable state is based on the rapid depletion of protein C due to its half-life of 6–8 hours. Warfarin’s mechanism of action is through inhibition of vitamin K-dependent clotting factors. In addition, protein C and protein S, which are natural anticoagulants, are also depressed due to their vitamin K dependence. Anticoagulant effects occur sooner with unfractionated heparin (UFH) and low molecular weight heparins (LMWHs) due to their short half-lives (ie, rapid steady state) and the short half-lives of the factors they inhibit.

It may take 4 to 6 days for a patient to become therapeutic when warfarin is used as a single agent. This is due to the variability of the half-lives of the clotting factors and warfarin’s long half-life. Upon initiation of warfarin, protein C is quickly depleted, leaving the patient naturally and therapeutically at risk for thrombosis. However, published literature does not support this risk.

Studies have shown that recurrence of thrombosis occurs at the same rate, despite early or late warfarin initiation with concurrent heparin. Hull and colleagues showed that 5 days of intravenous heparin with early initiation of warfarin on day 1 of treatment (short-course) was as effective as 10 days of heparin with day-5 initiation of warfarin (long-course). They determined that the recurrence of thrombosis was 7.0% in the long-course therapy compared to 7.1% with the short-course group. Gallus and colleagues assessed day-1 warfarin treatment compared to day-7 warfarin treatment and also found similar rates of recurrence for both groups, 3.6% and 4.7%, respectively. Thus, these data do not support an increased risk of thrombosis recurrence when beginning warfarin on day 1 with heparin therapy in the setting of a controlled clinical trial.

In addition, numerous studies have documented a shortened LOS with early initiation of warfarin. One small, retrospective study assessed LOS with warfarin started within 24 hours of heparin compared to starting 24 hours after heparin and determined that LOS was decreased by 2 days for the early start group. A similar study showed a 2.2-day decrease in LOS with early initiation of warfarin.

A caveat to applying the results of the above studies is that in a controlled setting patients may be adequately anticoagulated with UFH sooner due to strict observance of treatment protocols. Current data collected at Shands at UF suggests that roughly 50% of patients receiving the institution-approved DVT/PE UFH weight-based treatment protocol do not achieve timely therapeutic anticoagulation (ie, within 24 hours) due to inappropriate protocol adjustments. Before initiating day-1 warfarin and heparin treatment, we first need to improve day-1 therapeutic UFH use by being more compliant with the UFH protocol. Another option for day-1 treatment would be to combine warfarin with therapeutic doses of LMWHs, which achieve therapeutic anticoagulation after the first dose. However, the drawbacks with this treatment approach are the lack of known dosage adjustments for renal failure and the prolonged duration of effect when overdoses are given.

A second concern about the early initiation of warfarin with UFH for DVT or PE is that UFH is insufficient during oral anticoagulation administration. The guidelines recommend that UFH be discontinued when the INR is stable and above 2, which typically occurs within 5 to 7 days of concomitant anticoagulation therapy. The theory supporting the use of at least 5 days of overlapping UFH is that warfarin’s anticoagulant effects are typically delayed for 4 days until all clotting factors are therapeutically depressed. By continuing UFH until warfarin has depressed the vitamin K-dependent clotting factors, (ie, 5 to 7 days), it ensures that patients are adequately anticoagulated. In order to set a goal discharge of 5 days post DVT/PE diagnosis, warfarin must be started on treatment day 1 to achieve 2 therapeutic INRs before discharge. However, improved compliance with the heparin protocol is needed before this can be instituted. Then, early administration of warfarin for thrombosis treatment could decrease LOS and provide hospital beds for needy patients.

**POLICIES AND PROCEDURES**

**Automatic approval for “Patient May Take Own Meds”**

When a patient is admitted, the admitting physician prescribes those home medications that are needed during the patient’s hospitalization. If the drug is listed in the Formulary, the drug is dispensed. If the drug is not listed in the Formulary, we do not have a supply from a previous nonformulary request, the drug is dispensed. However, there are nonformulary medications that are not available.

Rather than go through the complete nonformulary process, the easiest solution to continue a patient’s home medication is to use their own supply, if they brought their prescriptions from home. In the past, a pharmacist had to page the prescriber, describe the situation, and get an order for the patient to continue his or her own supply of medication. Since this is universally approved, the P&T Committee approved a “P&T-Authorized” order to allow the patient to use his or her own supply of medication in this circumstance.

In order for this process to be implemented, a complete order must be written (eg, drug, strength, route, and frequency). Orders like, “May take home meds” will not be accepted. Like all orders allowing patients to take their own supply of medication, the product will have to follow the “Patient Medications Brought Into Shands at the University of Florida” policy (http://intranet.shands.org/lccace/Intranet/Patient%20Care/PM02-37.pdf). A pharmacist has to be able to verify that the contents of the prescription vial are the same as the drug listed on the label of the vial. Patients cannot use their own supply of a controlled substance. If these products cannot be switched to a product listed in the Formulary, then (continued on next page)
Dietary supplement use in the hospital

The policy that allows physicians to prescribe dietary supplements for their inpatients has been modified based on recent developments regarding the certification of these products. Currently, there are no dietary supplements listed in the Formulary, and patients may only use their own supply from a sealed container. Inpatient supplement use requires a written order so that these products are listed with the patient’s medications on the medication administration record (MAR), and so they can be screened for potential drug interactions.

Until recently, there has been no way to assure the contents of a dietary supplement container were safe. However, there are now USP-verified dietary supplements that have been rigorously tested and meet the United States Pharmacopeia’s standards. Supplements meeting these standards contain the supplement(s) listed on the label in the amount listed (ie, integrity). These supplements do not contain harmful levels of contaminants (ie, purity). This certification also assures that the product will break down appropriately for absorption in the body (ie, dissolution) and is made under good manufacturing processes (ie, safe manufacturing). Products meeting these standards will have the USP-verified dietary supplement seal on each bottle.

This is a major change for dietary supplements. Over the last decade, despite widespread use of these products, consumers have had no legitimate assurance that the product being taken was the product and amount listed on the label. There are numerous reports in the literature of products not containing any of the labeled product and/or containing contaminants. For this reason, the P&T Committee would not consider the addition of any dietary supplement in the Formulary. These products were deemed unsafe.

Now that there is a list of products that are USP-verified, these products could be considered for addition in the Formulary. Products meeting these standards will have the USP-verified dietary supplement seal on each bottle. This is a major change for dietary supplements. Over the last decade, despite widespread use of these products, consumers have had no legitimate assurance that the product being taken was the product and amount listed on the label. There are numerous reports in the literature of products not containing any of the labeled product and/or containing contaminants. For this reason, the P&T Committee would not consider the addition of any dietary supplement in the Formulary. These products were deemed unsafe.

Currently, the list of USP-verified dietary supplements is small. The following products are available: alpha lipoic acid, coenzyme Q10, fish oil, Echinacea (purnpura), ginseng, L-lysine, lutein, and methylsulfonylmethane (MSM).

The USP web site lists brands of USP-verified supplements (http://www.usp.org/USPVerified/dietarySupplements/resources.htm).

A good source of evidence-based information on the use of these dietary supplements can be found on the web at http://www.nlm.nih.gov/medlineplus/druginformation.html.

Policies and procedures, from page 3 a nonformulary request will have to be made. Nonformulary schedule II controlled substances are difficult to obtain because of regulatory requirements and a significant delay should be expected.

In general, patients’ own supplies of injectables, liquids, and topical products cannot be used (unless explicitly allowed by the policy cited). It is difficult to identify these products and assure safe use.