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B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met February 15, 2011. 6 products were added in the *Formulary*, and 3 were deleted. 7 products were designated nonformulary and not available. 1 interchange and 3 restrictions were approved. 1 drug was designated a high-priority nonformulary drug to facilitate acquisition, if needed.

◆ ADDED

Buprenorphine Sublingual Tablets (Generic)*

**Restricted*

Buprenorphine Transdermal (Butrans® by Purdue Pharma)*

Ceftaroline (Teflaro® by Forest Laboratories)*

**Restricted to ID or Anti-Infective Management Program Approval*

Guanfacine Tablets (Generic)

Guanfacine ER Tablets (Intuniv® by Shire)*

**Restricted to continuation of therapy from home*

Insulin, Regular, Concentrated, U-500 (Humulin® R U-500)

**Restricted to Pharmacy Administration Approval*

◆ DELETED

Beractant (Survanta®)†

†Nonformulary and Not Available

Buprenorphine-Naloxone (Suboxone®)†

Sodium Chloride 5% 500-mL IV Bag (Generic)†

◆ NONFORMULARY AND NOT AVAILABLE

Aliskiren-Amlodipine-Hydrochlorothiazide (Amturnide®)

(continued on next page)

NOTICE

Proposal: Delete IV Phenergan® from the *Formulary*

The P&T Committee will be considering whether to prohibit the use of intravenous (IV) promethazine [Phenergan®] at Shands at UF at the April P&T Committee meeting. If adopted, use of the IV route of promethazine would be prohibited, effective June 1, 2011. May 2011 would be a transition month, when prescribers would be notified of the deadline and apprised of the various alternatives. A transition month is used when there is a major change that affects many prescribers.

Attending physicians who would like to have input in this decision should send their comments in writing to hatton@ufl.edu by March 29, 2011. If you send evidence to support your position, it is more likely you will have an impact on the P&T Committee's final decision. If you would like to be present at the P&T Committee meeting for this discussion, you will need to complete a *Disclosure Form.* Information about attending the meeting and completing a *Disclosure Form* can be obtained via the email address above.

The P&T Committee is considering prohibiting the use of IV promethazine because it can cause patient harm, such as damage to blood vessels and surrounding tissues. The Institute for Safe Medication Practices (ISMP) has been recommending various strategies to try to minimize the risks of patient harm.[1] Extravasation and inadvertent intra-arterial injection has resulted in burning, pain, swelling, severe vessel spasm, thrombophlebitis, thrombosis, phlebitis, nerve damage, paralysis, abscess, tissue necrosis, and gangrene. Fasciotomy, skin grafts, and even amputations have been required from the tissue damage caused by intravenous promethazine.

There are various strategies used to promote patient safety. These range from less effective strategies, like education, to more effective strategies, like blocking strategies (ie, removal from the *Formulary*). There have been several educational articles previously published in the Bulletin.[2-3] There is an opportunity to institute more effective strategies to promote the safe use of antiemetics.

A medication safety strategy that lies in the middle is labeling, which instructs nurses to dilute promethazine, administer at a slow rate, and administer only in large veins. Education and labeling are known to be less effective than forcing or blocking strategies.

If IV promethazine is no longer available, what are the alternatives? We use a high volume of IV promethazine, so it is difficult to work with a small group of prescribers to provide alternatives. Thus, we are making this proposal to obtain input from as many prescribers as possible. Alternatives include different routes of promethazine (ie, oral, suppositories, and "deep" intramuscular), ondansetron, and prochlorperazine (Compazine®). Prochlorperazine is probably the closest alternative to promethazine; however, it is not as irritating to veins and tissues. Although there is little data to directly compare these agents, there is a perception that prochlorperazine is less sedating but has a slightly higher rate of dystonic reactions.

In addition to concerns about tissue damage, promethazine also has a black-box warning that states its use is contraindicated in children less than 2 years of age and advising caution in children 2 years and above due to a potential risk for fatal respiratory depression. Prochlorperazine carries a similar warning.

If you would like to try prochlorperazine as an alternative to promethazine, prochlorperazine 5 to 10 mg equals promethazine 6.25 to 12.5 mg.

REFERENCES

1. Anon. Action needed to prevent serious tissue injury with IV promethazine. ISMP Medication Safety Alert. August 10, 2006.
2. Dunham M. Resolve to dilute. Drugs & Therapy Bulletin 2007;21(1):3-4.
3. Logan J. Prochlorperazine – The forgotten antiemetic. Drugs & Therapy Bulletin 2009;23(6):1,6.

Formulary update, *from page 1*

◆ **NONFORMULARY AND NOT AVAILABLE (CONT.)**

Drospirenone-Ethinyl Estradiol-Levomefolate (Safyral®)

Fentanyl, Sublingual (Abstral®)

Poractant (Curosurf®)

◆ **HIGH-PRIORITY NONFORMULARY DRUGS**

Carglumic Acid (Carbiglu®)

◆ **INTERCHANGES**

Buprenorphine (Generic) for **Buprenorphine-Naloxone** (Suboxone®)

◆ **CRITERIA-FOR-USE CHANGES**

Buprenorphine Sublingual Tablet (Generic)*

Buprenorphine Transdermal (Butrans®)*

**Restricted to continuation therapy from home only.*

Ziprasidone IM (Geodon®)*

**Restricted to Psychiatric Unit and the ED with a 3-day stop order.*

Buprenorphine is a partial mu-agonist and kappa-antagonist that has been used as an analgesic in the United States for more than 25 years. It is currently available in multiple dosage forms, including injectable and sublingual formulations, both with and without naloxone. The latest formulation, **transdermal buprenorphine** (Butrans®), was approved by the FDA in July 2010 and was recently marketed. Injectable buprenorphine has not been listed in the *Formulary* since the 1980s. **Sublingual buprenorphine-naloxone** (Suboxone®) has been listed in the *Formulary* and was restricted to opioid addiction therapy and for chronic pain with a history of opioid dependency at Shands Vista. Use at Shands at UF has been limited to continuation of therapy only.

There are limited data on the use of sublingual buprenorphine in the management of chronic pain, with the majority of positive data generally coming from small, open-label studies. The efficacy of transdermal buprenorphine has been demonstrated in multiple randomized, placebo-controlled trials. However, available literature on dosages from 5-20 mcg/hr is limited.

Serious adverse events associated with this drug include respiratory depression, QT prolongation, and CNS depression. The most common adverse effects seen are similar to those of other opioids, and include nausea, headache, dizziness, and constipation. Buprenorphine should be used with caution with benzodiazepines or muscle relaxants as respiratory depression may worsen.

Currently, only sublingual buprenorphine without naloxone (Subutex®) is available as a generic. Butrans® has a labeled indication for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period. Butrans® is much more expensive than its alternatives, which are available as generics.

The use of oral buprenorphine for chronic pain at Shands Vista has been problematic when a patient's third-party payer will not cover treatment after discharge. Thus, both oral and transdermal buprenorphine can be used ONLY for patients who can continue treatment after discharge. Transdermal buprenorphine is approved only for continuation of home medication use. Patients cannot use their own supply from home (ie, it is a controlled substance). We are developing guidelines for transitioning to other options while patients are hospitalized. Butrans® should not be started in the inpatient setting. This applies to both Shands at UF and Shands Vista.

The criteria for the use of sublingual buprenorphine were revised. For both Shands at UF and Shands Vista, the approved criteria for use for chronic pain include the following. Initiation of therapy must be done by a physician with pain medicine certification or the Pain Service. Continuation of home medication use is appropriate for treatment of opioid addiction or chronic pain. The initial order must include the indication for use.

When sublingual buprenorphine is used for the treatment of opioid addiction, initiation of therapy must be ordered by a prescriber with addiction medicine certification. Again, the initial order must include an indication for use and the chart documentation of a recognized comprehensive treatment program is required. The prescriber must have DATA 2000 waiver ID number or "X" number as required by DEA.

Since buprenorphine is now available as a generic and Suboxone® is not, an automatic conversion from Suboxone® to generic sublingual buprenorphine was approved for inpatients. Buprenorphine tablets replace Suboxone® as the formulary agent and Suboxone® was designated nonformulary and not available. Shands Vista day-stay patients are exempt from automatic conversion and will continue to receive Suboxone®.

Ceftaroline is a derivative of a 4th-generation cephalosporin with increased activity against methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MRSA). It has similar gram-positive coverage to ceftriaxone and cefotaxime with more gram-negative coverage. It has activity against Enterobacteriaceae. Ceftaroline has limited or no activity against gram-negative bacteria associated with healthcare infections (eg, Pseudomonas). It has a labeled indication for the treatment of acute bacterial skin and skin structure infections and community-acquired pneumonia (CAP).

In clinical trials, ceftaroline (600 mg IV q12 hours) was shown to be non-inferior to standard regimens in patients with skin and skin structure infections and CAP. Ceftaroline was shown to be well tolerated. Common adverse events include diarrhea, headache, nausea, and hypokalemia. In addition, seroconversion from negative to positive direct Coomb's test occurred in approximately 11% of patients who received ceftaroline. During the clinical trials, no patients developed hemolytic anemia. The mechanism of the conversion is not known, but this effect should be considered by prescribers.

Ceftaroline is an alternative to standard regimens for the management of skin and skin structure infections and CAP. The cost of ceftaroline is about 2-4 times more expensive than our standard regimens. Since ceftaroline is not associated with clinical improvement over standard regimens, it was restricted to Infectious Diseases and the Antimicrobial Management Program for the management of resistant gram-positive organisms; second-line use for the management of MRSA and penicillin-resistant *Streptococcus pneumoniae* (PRSP) defined as treatment of MRSA infections in patients who fail primary therapy (ie, vancomycin), patients with polymicrobial infections that are susceptible to ceftaroline, and as an alternative for patients who are intolerant to vancomycin (eg, nephrotoxicity). Ceftaroline is not indicated in children, patients with cystic fibrosis, and for combination therapy with other beta-lactams.

Guanfacine is an alpha-agonist used as an alternative to stimulants in the management of attention-deficit/hyperactivity disorder (ADHD). **Intuniv®** (guanfacine ER) and immediate-release guanfacine tablets were reviewed proactively due to relatively high nonformulary use, especially at Shands Vista.

The exact mechanism of action of guanfacine in the treatment of ADHD is not fully understood; however, it is thought that the activity on postsyn-

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Formulary update, *from page 2*

aptic alpha$_{2a}$ receptors in the prefrontal cortex contribute to its therapeutic efficacy. The IR and ER formulations have slightly different pharmacokinetic properties.

The guanfacine ER product received Food and Drug Administration (FDA) approval in September 2009 for use in children 6 to 17 years old for the management of ADHD. The IR formulation does not have this labeled indication, but is used off-label in ADHD. It is also used in the treatment of ADHD with comorbid tic disorders and to treat hyperactivity and impulsivity in children with pervasive development disorders (PDD), including autism. Doses for both formulations start low and are titrated to effect; guanfacine IR is titrated every 3-4 days and Intuniv® is titrated every 7 days. Higher doses on a mg/kg basis are associated with improved efficacy; however, doses above 4 mg/day have not been studied. Abrupt discontinuation is not recommended and may result in withdrawal symptoms like nervousness, anxiety, and rebound hypertension.

Unfortunately, there are no head-to-head trials comparing guanfacine with other ADHD medications. There have been several large, placebo-controlled clinical trials establishing the safety and efficacy of guanfacine ER for the treatment of its labeled indication for ADHD. Smaller studies with guanfacine IR have also indicated favorable treatment of ADHD symptoms especially in situations with comorbid tic disorders. There is no head-to-head comparison of the ER and IR formulations.

While ADHD is generally managed in the outpatient setting, there are situations where it is used inpatient. Due to the need for continuity of home medication to prevent symptoms of withdrawal and specific labeling recommendations not to interchange ER and IR formulations, Intuniv® was added in the *Formulary* for continuing home therapy. Given the proven efficacy of guanfacine IR, it was also added in the *Formulary*. Studies are needed to describe how best to more rapidly convert between the IR and ER formulations and vice versa.

Concentrated regular insulin U-500 was evaluated proactively because of concerns about the safety of nonformulary use. There are, occasionally, patients admitted on this insulin strength. There is concern about the best method of handling this drug, since it has been associated with serious medication errors.

The American Diabetes Association (ADA) released a statement in 2005 regarding the use of U-500 insulin in patients with extreme insulin resistance. When insulin doses exceed 0.5-1 units/kg/day, the volume of U-100 may become an issue. When doses are greater than 3 units/kg/day, volume is difficult to administer subcutaneously and can be resolved with the use of U-500 insulin. According to the ADA algorithm, patients requiring greater than 200 units of insulin daily should exclusively use U-500. The algorithm is based on units of insulin administered per dose with increases based on patient-specific requirements. In patients requiring greater than 2000 units of insulin, delivery of U-500 with an infusion pump should be considered. There have been patients admitted to Shands at UF on pumps requiring U-500 insulin.

Severe insulin resistance may be found in many conditions, including obesity, stress, endocrine-related disorders, genetic defects of the insulin receptor gene, and insulin receptor antibodies. U-500 concentrated regular insulin is equivalent to 5 times the potency of regular insulin.

The Institute for Safe Medication Practices (ISMP) has emphasized reports about U-500 insulin being mistaken for U-100 insulin. These mistakes occurred when U-500 was accidentally chosen from the computer screen. Major suppliers of drug information systems have added "concentrated" preceding "U-500" to decrease these errors.

If "concentrated" is not present with the insulin U-500 description, ISMP recommends listing it separately from other insulins so that they are on a different page. They also suggest adding a hard stop to all orders for insulin U-500 so prescribers and pharmacists verify that the order is appropriate for the patient. Pharmacy administrative approval will be this "hard stop" at Shands at UF.

Another concern with insulin U-500 is the difference in units/milliliter from insulin U-100; the 2 products do not have the equivalent number of units per milliliter. Insulin syringes have unit markings specific to 100 units/mL. Insulin U-500 should be administered with tuberculin syringes that have volume markings. The dose of insulin U-500 should be ordered with the specified volume in addition to the number of units.

There are no guidelines available for converting patients from U-500 insulin to U-100 insulin. However, if the severe insulin-resistant state is transient and the patient is receiving U-500, it is possible to taper the insulin and switch back to U-100. For instance, patients requiring greater than 200 units daily should exclusively receive U-500, however, if their insulin requirements decrease to less than 175 units daily patients could switch back to U-100.

The onset, peak, and duration of action differ between U-100 and U-500. U-100 has a peak effect around 2 to 4 hours following administration with a duration of action of 5 to 7 hours. U-500 has a longer duration of action similar to NPH insulin; its duration can be up to 24 hours due to the concentration of the insulin. The effects of regular and NPH insulin can vary according to the volume of the dose; larger doses can cause a delay in the peak with an extended duration of action.

U-500 insulin was added in the *Formulary* with extensive safeguards to be put in place to prevent medications errors. It will not officially be listed in the *Formulary* until March 15, 2011, in order to establish the appropriate safeguards. In addition to pharmacy administration approval for each patient, only 1 vial will be kept in the IV Center Omnicell cabinet [like a controlled substance], and the IV Center will pull up each dose for each patient. The Medication Safety Committee will review these procedures over time and recommend modifications, if needed.

Beractant, **calfactant**, and **poractant** are natural lung surfactants. Beractant and calfactant come from a bovine source, while poractant is a porcine product. These products are all labeled for the treatment of respiratory distress syndrome (RDS) in premature neonates. Premature neonates lack the natural surfactant needed to improve lung function.

Beractant and calfactant have been listed in the *Formulary*. Poractant was nonformulary. After consulting with the Department of Pediatrics, beractant was deleted from the *Formulary*. Both beractant and poractant were designated nonformulary and not available.

500-mL IV bags of **sodium chloride 5%** were deleted from the *Formulary* and designated nonformulary and not available. This strength of sodium chloride was not being used, and sodium chloride 3% IV remains listed in the *Formulary*.

Hypertonic sodium chloride [saline] is used in the treatment of hyponatremia and cerebral edema. Because these agents are irritating to veins, they are generally given via a central line. These products are considered high-alert medications because of the potential to cause harm (eg, confusion with lower concentrations of sodium chloride). Deaths have been reported from the inadvertent administration of hypertonic saline.

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Formulary update, *from page 3*

5% saline can be confused with 0.45% [half] normal saline.

Amturnide® is a combination antihypertensive drug containing the renin inhibitor **aliskiren**, the dihydropyridine calcium channel blocker **amlodipine**, and the diuretic **hydrochlorothiazide**. Amlodipine and hydrochlorothiazide are listed in the *Formulary,* however, aliskiren has previously been designated nonformulary and not available.

Amturnide® has a labeled indication for the treatment of hypertension, but it is not indicated for initial therapy. FDA approval of Amturnide® continues the trend of more fixed-dose combinations of antihypertensive agents being marketed. In general, combination products are not listed in the *Formulary.*

Safyral® is an oral contraceptive with labeled indications for the prevention of pregnancy and to raise folate levels. **Drospirenone**, which is an analogue of spironolactone, is the progesterone component of this combination oral contraceptive. It has antimineralocorticoid and anti-estrogenic properties. Drospirenone is also found in Beyaz® and Yaz®. **Levomefolate** is also known as L-methylfolate, and is the biologically active form of folate. Like most combination oral contraceptives, **ethinyl estradiol** is the estrogenic component of Safyral®.

Safyral® was designated nonformulary and not available. Patients should use their own supply from home. Most oral contraceptives are not listed in the *Formulary.* A generic version of Lo-Ovral® is listed to begin therapy on patients who are being started on oral contraceptives to decrease their bleeding risks.

Abstral® is a **sublingual** dosage form of **fentanyl** that has a labeled indication for breakthrough cancer pain. Since it was designated nonformulary and not available and it is a controlled substance, patients may not use their own supply from home.

Carglumic acid is a carbamoyl phosphatase synthetase 1 (CPS1) activator with labeled indications for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) and for maintenance therapy for chronic hyperammonemia due to the deficiency of NAGS. NAGS deficiency is a rare disorder; and, therefore, its safety and efficacy was evaluated in only 23 patients before it was approved by the FDA. Only a few cases of NAGS have been reported worldwide and the overall incidence is unknown. NAGS is one of several urea cycle disorders.

Carglumic acid is available from Accredo, and Shands will purchase it only if a patient is admitted and cannot provide their own supply. It is very expensive and has a short shelf-life. A 5-tablet bottle costs $685 ($137 per tablet), while a 60-tablet bottle costs $8220. Bottles must be discarded 1 month after opening. The 60-tablet bottle will not be purchased for inpatient use.

By designating carglumic acid a high-priority, nonformulary drug, instructions on how to obtain the drug will be created in our computer systems.

Ziprasidone IM is the intramuscular formulation of the atypical antipsychotic ziprasidone. It has a labeled indication for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need IM antipsychotic medication for rapid control of agitation.

Patients at risk for QT prolongation should not receive ziprasidone. It should be used cautiously in patients receiving other QT-prolonging drugs, and patients receiving this drug should be monitored. A 3-day stop order was approved to prevent the continued use of the IM route of administration. IM ziprasidone can only be used in the Psychiatric Unit and the Emergency Department.