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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met August 19, 2008. 2 drugs were added in the *Formulary*, 1 for a 4-month evaluation. 3 drugs were deleted, and 4 were designated nonformulary and not available. 2 interchanges were approved, and 1 drug was added to the Chemotherapy Policy.

◆ ADDED

Desflurane (Suprane® by Baxter)*

**Added for a 4-month evaluation*

Fosaprepitant Injection (Emend® by Merck & Co)†

†Restricted to clinical pharmacist approval (like aprepitant)

◆ DELETED

Cromolyn Inhalation Solution (Generics)‡

‡Nonformulary and not available

Phenytoin Injection (Generics) ‡§

‡§Nonformulary and not available; Interchanged to Fosphenytoin Injection

Stannous Fluoride Gel (Generic)‡

‡Nonformulary and not available

◆ NONFORMULARY AND NOT AVAILABLE

Glycerol, Sterile Anhydrous (Compounded)

◆ THERAPEUTIC INTERCHANGES

CiproDex® (Ciprofloxacin + Dexamethasone) **for Cipro® HC** (Ciprofloxacin + Hydrocortisone)¶

¶4 drops CiproDex® for 3 drops of Cipro® HC

Fosphenytoin (Generics) **for Phenytoin Injection** (Generics)**

***Same dosage in phenytoin equivalents*

◆ CRITERIA-FOR-USE CHANGES

Bendamustine (Treanda®)††

††Added in the Chemotherapy Policy

(continued on next page)

POLICIES AND PROCEDURES

New pediatric anticoagulation policies

At the June P&T Committee meeting, a new Anticoagulation Monitoring Policy was approved. This policy made several changes, which are required by the Joint Commission (TJC). All hospitals accredited by TJC must comply with the National Patient Safety Goals (NPSGs) for Anticoagulation (ie, Requirement 3E). This initiative is intended to reduce the likelihood of patient harm associated with the use of anticoagulation therapy, which has long been recognized as a high-risk medication. These requirements promote the use of standardized practices.

When the anticoagulation policy was approved in June, it did not include protocols for use in children. At the August P&T Committee, 2 policies were approved based on the patient's age: *Pediatric Heparin Protocol for Patients Less than 12 Years of Age* and *Pediatric Heparin Protocol for Patients Older Than or Equal to 12 and Less than 18 Years of Age*. These protocols are limited to the Pediatric Intensive Care Unit (PICU) or Intermediate Care Units (IMCs). Heparin will be provided only in a standard concentration (ie, 100 units/mL), with the size of the bag determined by the patient's age (ie, 50 mL or 250 mL). There is a standard loading dose (ie, 80 units/kg) and standard starting dosage (ie, 18 units/kg/hr).

Standard monitoring includes the use of unfractionated heparin levels with adjustments to the dosage based on the measurements. The target heparin level is 0.3 to 0.7 units/mL. Additional monitoring is specified (eg, daily CBC and platelet count) with guidelines for notification of the prescribing physician (eg, when bleeding occurs or platelet counts drop).

The approval of the pediatric heparin protocols maintains our efforts to be ahead of TJC's 2008 National Patient Safety Goals for Anticoagulation.

Therapeutic interchange – 2008

A drug is ordered, but a different drug is dispensed and administered. The drug that is dispensed is not a generic equivalent of the ordered drug, but it is a "therapeutically equivalent" product. A single drug product is selected and listed in the *Formulary* for a therapeutic class. The drugs are not the same, but they are so similar that there is no clinically significant difference among the drugs in a class. All non-selected drugs are changed to the formulary class representative. The non-selected drugs are nonformulary and are not available—with a few exceptions.

This is therapeutic interchange. Therapeutic interchange is the substitution of various therapeutically equivalent drug products by pharmacists under arrangements of the authorized prescribers who have agreed on the conditions for the change.

Therapeutic interchange is reviewed and approved by the medical staff by the Pharmacy & Therapeutics (P&T) Committee, which is a medical staff committee. Representatives from various medical specialties participate in the P&T Committee. If a drug class is used by a specific medical specialty and a representative from that medical specialty is not on the P&T Committee, the department head is contacted to

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INSIDE THIS ISSUE

Formulary update, *from page 1*

Desflurane is an inhaled anesthetic gas that was re-evaluated as a possible replacement for sevoflurane at the Shands Florida Surgical Center (SFSC). Desflurane and sevoflurane are volatile liquid anesthetic agents that are vaporized to a gas and used for general anesthesia in combination with other gases (eg, oxygen) and intravenous (IV) anesthetic agents (eg, propofol or opioids). Because the post-operative recovery of these agents is more rapid than with isoflurane, they may be preferred in the outpatient surgery setting (although the time advantages of these shorter-acting, but more expensive, agents is controversial because other issues usually slow the post-operative recovery process).

A meta-analysis of articles published through 2003 comparing desflurane and sevoflurane found minor differences in recovery time in the operating room (OR) (ie, 1.2 minutes), time to obey commands (ie, 1.7 minutes), time to extubation (1.3 minutes), and time to orientation (1.8 minutes). However, no significant differences were detected in the phase I or II Post-Anesthesia Care Unit (PACU) recovery times or in the rate of post-operative nausea and vomiting (PONV). The clinical significance of these small differences has been questioned. Studies published since this meta-analysis validate these findings.

The adverse effects associated with desflurane are the same as those associated with isoflurane and sevoflurane. Like all inhaled anesthetic gases, desflurane is associated with more PONV than propofol; however, the incidence of PONV is similar between desflurane and sevoflurane. Desflurane is the most pungent agent, with respiratory irritation seen above 1 minimum alveolar concentration (MAC). Therefore, desflurane is not used for mask inductions. At low flow rates, there is concern about nephrotoxicity with sevoflurane because of a fluorinated metabolite called Compound A; however, there are no reports of Compound A toxicity in humans.

Independent assessments of cost suggest that desflurane is more expensive than sevoflurane. Desflurane is available only from a single vendor and requires a special vaporizer for administration, which can add to expenses. It has been suggested that the per-MAC-hour cost at a lower flow rate for desflurane (ie, 1 mL/hr) can be compared with a higher flow rate for sevoflurane (ie, 3 mL/hr). If this can be accomplished, it would lower costs. However, using a lower flow rate with desflurane will require extra effort to maintain adequate anesthesia.

Therefore, desflurane was added in the *Formulary* for a 4-month evaluation (ie, September through December). Its use was restricted to the SFSC. If overall use of inhaled anesthetics and propofol decrease during this time, then desflurane will be permanently added in the *Formulary* and remain restricted to SFSC. If overall costs are increased, conversion back to sevoflurane will occur.

Fosaprepitant is a new pro-drug ester of aprepitant that can be given by injection. Aprepitant is an oral drug used for the prevention of chemotherapy-induced delayed nausea and vomiting. Injectable fosaprepitant has a labeled indication for the first dose in the 3-day regimen for the prevention of chemotherapy-induced nausea and vomiting.

Aprepitant was added in the *Formulary* and restricted to approval by an oncology pharmacist in August 2003. Like aprepitant, fosaprepitant was added in the *Formulary* and restricted to approval by an oncology pharmacist.

Cromolyn is a mast cell stabilizer. The solution for inhalation was used as a prophylactic agent for the prevention of mild to moderate asthma. The use of cromolyn by oral inhalation has been very limited due to the availability of superior agents.

King Pharmaceuticals discontinued the manufacture of Intal® (cromolyn solution for nebulization), and there is no other manufacturer of this product. The product has not been recalled from the market, and it may take several months before supplies stocked in community pharmacies are exhausted or go out of date. According to the letter from King Pharmaceuticals, the decision to discontinue this product was "based upon many factors, including [their] understanding of current medical therapy, and the availability of alternative asthma therapies." Therefore, effective immediately, cromolyn sodium solution for inhalation has been deleted from the *Formulary* and designated nonformulary and not available. Cromolyn nasal spray (Nasalcrom®) remains listed in the *Formulary*.

Intravenous phenytoin was designated nonformulary and not available and will be interchanged to an equivalent dosage of fosphenytoin in phenytoin equivalents. The implementation date for this interchange will be October 1st.

The decision to eliminate the use of IV phenytoin came after the restrictions were lifted from fosphenytoin injection at the June P&T Committee meeting. The Department of Pediatrics expressed their support for an automatic interchange to fosphenytoin for children. Rather than have separate systems for adults and children, the proposal was evaluated for all patients.

An article was published in the July-August issue of the *Drugs & Therapy Bulletin* announcing the proposal to delete phenytoin injection from the *Formulary*. Only 1 comment was received, and it was supportive of the deletion and interchange.

Stannous fluoride is a topical agent used for the prevention of dental caries or for dental desensitization. This product has not been used at Shands at UF, Shands Vista, or Shands Rehab Hospital. Because of lack of use, stannous fluoride gel was deleted from the *Formulary* and designated nonformulary and not available.

Sterile anhydrous glycerol was originally evaluated by the P&T Committee in April 2005 for possible addition in the *Formulary*. It was requested for use by radiologists for chemical rhizotomies, which are nerve ablations used in the treatment of trigeminal neuralgia.

Since there is no commercially available product, sterile anhydrous glycerol would have to be obtained from an outside compounding pharmacy that compounds sterile products from non-sterile ingredients. It can be obtained only on a patient-specific basis and cannot be added in the *Formulary.* In order for sterile anhydrous glycerol to be used nonformulary, a patient would have to give informed consent. This informed consent document has not been developed; therefore, sterile anhydrous glycerol was designated nonformulary and not available.

In January 2005, **CiproDex®** was added in the *Formulary* and **Cipro HC®** was deleted and designated nonformulary and not available. CiproDex® has a labeled indication for otitis media with tympanostomy tubes and otitis externa. Otic fluoroquinolone suspensions are used for various off-labeled otic infections for which there is little scientific evidence of efficacy. However, the otitis media data are considered applicable for other otic infections.

Evidence shows that ciprofloxacin combined with a topical steroid significantly increases clinical cure rates when compared with monotherapy for the treatment of acute otitis media with otorrhea through tympanostomy tubes. Topical steroids are added to fluoroquinolones to reduce inflammation and enhance clinical response rates.

An additional benefit for CiproDex® is that it is a sterile product. Cipro HC® is not sterile. Despite this information, Cipro HC® continues to be ordered even though it is not available. Therefore, CiproDex® will now be automatically interchanged for Cipro HC® using 4 drops of CiproDex® for 3 drops of Cipro HC®.

Bendamustine is an oral cytotoxic drug with alkylating agent and purine analogue actions. It has a labeled indication for the treatment of chronic lymphocytic leukemia (CLL). It may have off-labeled uses for non-Hodgkin's lymphoma, multiple myeloma, breast cancer, or other cancers. Bendamustine was not added in the *Formulary,* but it was added to the Chemotherapy Policy. If requested for nonformulary use, bendamustine must be ordered on a Chemotherapy Order Form.

Why are insulin pens "less stable" than insulin vials?

Many hospitals have switched from using vials to using pens for various insulin products. Insulin pens have several advantages, including clear labeling on each pen (instead of using unlabeled syringes and a vial).[1] The pens are in a ready-to-use form and require less nursing time to prepare.[1] Pens are also a dosage form that allows diabetes educators to teach patients recently diagnosed with diabetes how to administer the insulin that they will use once they are discharged from the hospital. However, a disadvantage of insulin pens is the shorter stability of these products when they are "in use" and kept out of the refrigerator.[2-5] This can lead to product waste.

Unopened insulin vials and pens are stable until the expiration date on the vial or pen when stored in the refrigerator. A refrigerator maintains the temperature between 2° C and 8° C (36° F and 46° F). Once a vial or pen is "in use," it is no longer necessary to store the product in the refrigerator. The maximum time that multi-use vials (or pens) can be stored is 28 days according to product labeling and USP guidelines. This, of course, presumes that the vial will be stored at room temperature and that excursions from this temperature will not occur. Room temperature is thermostatically maintained between 20° C to 25° C (ie, 68° F to 77° F). Room temperature guidelines do allow brief exposures to temperatures as high as 40° C (ie, 104° F). The extreme heat of Florida or the freezing cold temperatures that many of us fled to Florida in order to avoid can affect the stability of insulin products that are "in use."

When stored at room temperature, insulin vials have "in-use" stabilities of 28 days, while pens are stable only for 7 to 14 days (ie, depending on the individual product's labeling). Therefore, insulin pens must be discarded after 10 days at Shands at UF (based on the shortest labeled stabilities of the pens that we stock). This has caused some to question why the insulin in pens is less stable than when it is stored in a vial. It turns out that this is a fairly difficult question to answer.[2-5]

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The shorter stabilities of insulin pens come from guidelines recommended by the FDA for insulin pens and cartridges. The recommendations in the guidelines for pens and cartridges differ from those for vials based on differences in the expected usage patterns for these products.

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According to pen manufacturers, stability guidelines established by the FDA for pens and cartridges consider 2 factors.[2,4] The first factor is the smaller volume and fewer total units of insulin supplied in the pen cartridge compared to a vial. The smaller volume is expected to lead to a more rapid exhaustion of the insulin in the cartridge compared to the vial. The other factor is the increased convenience of the pen. The increased convenience of the pen is expected to result in patients exposing their insulin to thermal and agitation conditions that would be greater than the exposure for insulin in vials.

The testing conditions used for determining the in-use dating for the cartridges are consistent with an expected increase in the thermal and agitation exposure of insulin in cartridges compared to insulin in vials. Thus, the testing conditions for vials and cartridges differ, which leads to different storage guidelines for vials and pens.

The current in-use storage recommendations for insulin pens are based on exposure to conditions that are severe and are not truly reflected by room temperature storage in the hospital setting. It is likely that insulin pens are stable for more than our current practice of dating pens and only using them for at most 10 days in the hospital setting. Official labeling of insulin pens in Europe have in-use stabilities of 21 to 28 days.[5] The current FDA standards are more stringent than those used in other countries.

Since most patients are hospitalized for less than 10 days, the waste of insulin pens often occurs when the patient is discharged and not based on short stability. Insulin pens dispensed to inpatients are not labeled for outpatient use and cannot be sent home with the patient.

Although it is unlikely that the true stability of insulin pens is only 10 days, there is no published evidence that allows use beyond the current official labeling of these products. Therefore, insulin pens must be dated when they are put in use and discarded after 10 days.

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Therapeutic interchange, *from page 1*
solicit input on that particular interchange.

Therapeutic interchange has been practiced for over 20 years at Shands at UF. Feedback from both attendings and housestaff consistently support the concept of interchanging to a product that is currently available, rather than constantly paging to have a new order written. Some institutions list only 1 agent in the class and constantly contact the prescriber to change the order to the formulary agent.

Since the medical staff are not contacted to write a new order, there has to be a mechanism to notify the medical staff and nursing when an interchange occurs. When a drug is prescribed that is interchanged, documentation of the interchange is placed in the chart. This documentation is placed in both the Physicians Orders section of the chart and the Progress Notes section. The notation in the Orders section notifies the patient's nurse of the change. The note in the Progress Notes notifies the medical staff.

There can be exceptions made to the interchange policy. If the patient has a rational reason not to receive the interchanged drug (ie, allergic to a dye in the interchanged product), the change can be overruled. Experience has shown that these situations are very rare.

A continually updated version of the drugs that are therapeutically interchanged can be found after logging on to the Shands Portal at https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Pharmacy/UF/Formulary/TherapeuticInterchange. Often when a new product is added to the list, prescribers are notified that beginning the next month an interchange will occur. This gives prescribers an opportunity to change their habits. Most prescribers use the preferred agents. Interchanges are relatively infrequent—once the housestaff and other prescribers know the drug that is listed as the "class representative."

Combination products also will be interchanged when the ingredients are listed in the *Formulary* and the exact amount of each ingredient is available. For example, an order for Vytorin® 10/10 will be changed to Ezetimibe 10 mg [Zetia®] and Simvastatin [Zocor®] 10 mg. The same documentation as for the therapeutic interchanges will occur.

There is concern that patients getting switched to a different drug during their hospitalization will be discharged on the new drug, then resume their old medication, resulting in therapeutic duplication and possible adverse effects. Prescribers must take this into consideration during the medication reconciliation process. When an interchange occurs, it is noted on the Transfer Medication Report and the medication administration record (MAR). Often, it is best to switch patients back to the medication they were admitted on, which may be preferred by the patient's third-party payer. The Home Medication Profile should always be reviewed when discharge medications are prescribed.