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B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met September 16, 2008. 3 drugs/dosage forms were added in the *Formulary*, and 1 dosage form was deleted. 6 drugs/dosage forms were designated nonformulary and not available. 2 interchanges were approved, and 1 criterion for use was revised.

◆ ADDED

Dexmedetomidine
(Precedex® by Hospira)*

**Restricted to specific off-labeled uses*

Factor VIIa, Recombinant
(NovoSeven® RT by Astellas)

Regadenoson
(Lexiscan® by Astellas)

◆ DELETED

Factor VIIa, Recombinant
(NovoSeven® by Astellas)†

†Removed from the market. Nonformulary and not available (after supplies exhausted)

◆ NONFORMULARY AND NOT AVAILABLE

Kinrix®
(Diphtheria, Tetanus, Acellular Pertussis, and Inactivated Polio Vaccine)

Pediarix®
(Diphtheria, Tetanus, Acellular Pertussis, Inactivated Polio Vaccine, and Hepatitis B Vaccine)

Pentacel®
(Diphtheria, Tetanus, Acellular Pertussis, Inactivated Polio Vaccine, and Hemophilus Influenza B Vaccine)

Rotavirus Vaccine (Rotarix®)

Rotavirus Vaccine (RotaTeq®)

(continued on next page)

MEDICATION USE EVALUATION

Conivaptan restriction

Conivaptan was added in the *Formulary* in June 2007 for the off-labeled use of normalizing serum sodium concentrations in patients who are hyponatremic and who need to go to the Operating Room (OR) within 96 hours. Due to the lack of data that demonstrates greater benefit of conivaptan therapy over other existing therapies, increased adverse events, drug interactions, and cost, conivaptan is restricted to approval by a clinical pharmacist. Patients qualify for conivaptan therapy if they are in an ICU/IMC and have low serum sodium concentrations that prevent them from going to the OR for a procedure. Conivaptan is not approved for use at Shands at UF for its labeled indication (ie, the treatment of euvolemic hyponatremia [eg, the syndrome of inappropriate secretion of antidiuretic hormone, or in the setting of hypothyroidism, adrenal insufficiency, pulmonary disorders, etc.] in hospitalized patients) because other measures are as effective and are less expensive.

Most patients could be managed with alternative measures and...the current conivaptan restriction is reasonable.

When conivaptan was added in the *Formulary*, the P&T Committee stipulated that its use would be evaluated after 12 months to evaluate the restriction process (ie, approval by a clinical pharmacist). From August 2007 through June 2008, there were 14 requests for conivaptan from 7 different services. Therapy was approved for 2 patients. Conivaptan was approved for a patient with heart failure who needed to go to the OR whose serum sodium was 120 mmol/L after failing continuous infusion furosemide therapy and fluid restriction. The patient's serum sodium increased by 1 mmol/L to 121 mmol/L after approximately 4 days of conivaptan therapy. Conivaptan was approved for another heart failure patient who needed to go to the OR whose serum sodium was 123 mmol/L. The patient received varying doses of furosemide therapy, 1-liter fluid restriction, and a 2-gram sodium diet without any improvement in the patient's serum sodium. This patient received only 0.1 mg of conivaptan therapy because he did not tolerate the infusion. The patient was placed on a 4-gram sodium chloride diet and continued to be on fluid restriction. Afterwards, his serum sodium increased by 7 mmol/L to 130 mmol/L approximately 24 hours after the initial therapy request.

Conivaptan requests were appropriately denied for 12 patients. Patients not eligible to go to the OR did not meet criteria. Several patients could be treated with 3% sodium chloride, oral sodium supplementation, avoidance of diuretics, or concentration of fluids. One patient had a spuriously low serum sodium level that was "corrected" by rechecking the level. Serum sodiums increased by an average of 5 mmol/L from the time of conivaptan request to 24 hours after the request. 11 of the 12 patients experienced an increase in serum sodium 24 hours after the initial conivaptan request. There was no change in 1 patient's serum sodium 24 hours after the initial conivaptan request. These data showed that most patients could be managed with alternative measures and that the current conivaptan restriction is reasonable.

Restriction of conivaptan therapy to clinical pharmacist-approval has saved approximately $35,000 over the period of evaluation.

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◆ **THERAPEUTIC INTERCHANGES**

Lidocaine Cream 4% (LMX®) **for Lidocaine-Prilocaine Cream** (EMLA®)

NovoSeven® RT (Factor VIIa, Recombinant) **for NovoSeven®** (Factor VIIa, Recombinant)‡

‡Automatic dose rounding to the new vial sizes

◆ **CRITERIA-FOR-USE CHANGES**

Conivaptan (Vaprisol®)§

§Maximum 12 hrs by peripheral line (ie, central line preferred) & prior approval by a clinical pharmacist

Dexmedetomidine is a relatively selective alpha$_2$-adrenoceptor agonist with centrally mediated sympatholytic, sedative, and analgesic effects. It has a labeled indication for sedation of intubated and mechanically ventilated patients during treatment in an intensive care setting. The labeling states that dexmedetomidine use should not exceed 24 hours. Dexmedetomidine has been on the US market since 1999.

Dexmedetomidine has been reviewed by the P&T Committee several times before, and each time it was designated nonformulary and not available. The P&T Committee previously determined that dexmedetomidine had no advantage for use in general ICU sedation compared with other agents.

The formulary status of dexmedetomidine was again assessed. This time dexmedetomidine was assessed for general ICU sedation, sedation during awake ventriculostomy placement, sedation during ventriculostomy placement in nonventilated patients, sedation during awake intubations, and sedation to aid in weaning patients off a ventilator.

The P&T Committee determined that the evidence still does not support the use of dexmedetomidine for general ICU sedation. Dexmedetomidine is approximately 38 times more expensive than midazolam and 10 times more expensive than propofol. Therefore, dexmedetomidine still will not be used for general ICU sedation.

However, the P&T Committee determined that dexmedetomidine should be added in the *Formulary* and restricted to use for awake ventriculostomy placements, ventriculostomy placements in nonintubated patients, and awake intubations. It was also designated an appropriate option for a 1-time use in agitated patients who have failed repeated attempts of weaning from the ventilator. This use will only occur based on strict criteria. Use to wean patients from the ventilator will be limited to a 12-hour infusion. There are limited data in the literature to support these indications (ie, case series at best); however, it was determined that there are no suitable alternatives for these uses.

In order to monitor the use of dexmedetomidine, a 6-month audit will be done. The P&T Committee will review these data to determine whether any changes are necessary to the current restrictions.

NovoSeven® RT is a new dosage form of **recombinant factor VIIa** that contains sucrose and L-methionine, which allow its storage at room temperature. The new formulation can be stored at room temperature (up to 77 degrees Fahrenheit) for up to 2 years. The original **NovoSeven®** product will no longer be marketed.

There are no differences in dosing or potency between the old and new products. Therefore, NovoSeven® was deleted from the *Formulary* and designated nonformulary and not available (when the supply is exhausted), while the new dosage form was added in the *Formulary*. NovoSeven® orders will automatically be interchanged to NovoSeven® RT

In April, the P&T Committee approved automatic dose rounding for NovoSeven®. Once a vial of factor VIIa is reconstituted, it has limited stability. A dose-rounding policy was approved to try to decrease waste that occurs when NovoSeven® was ordered but not subsequently used. Rounding doses to available vial sizes decreases waste.

NovoSeven® RT comes in vial sizes that are different than the old product. NovoSeven® RT comes in 1-mg, 2-mg, and 5-mg vial sizes, instead of the 1.2-mg, 2.4-mg, and 4.8-mg vial sizes for NovoSeven®. The new product is more concentrated (ie, 1 mg/mL instead of the old 0.6-mg/mL concentration).

Because of the change to NovoSeven® RT and the new vial sizes, the P&T Committee approved modification of the dose rounding protocol (see Table below). The largest rounding down (decrease) in the new protocol is 29% (1.4 mg rounded down to 1 mg), while the largest rounding down was 33% in the old protocol (ie, 1.79 mg rounded down to 1.2 mg).

Regadenoson is an A_{2A}-adenosine-receptor antagonist that dilates coronary vessels and increases blood flow. It is used as a pharmacologic stress agent in radionuclide myocardial perfusion imaging in patients unable to undergo an adequate exercise stress test.

Adenosine has been the primary pharmacologic stress agent listed in the *Formulary*. Adenosine is contraindicated in patients with bronchoconstrictive or bronchospastic lung disease. Regadenoson selectively activates A_{2A} adenosine receptors, which causes less bronchoconstriction. Regadenoson can be used in patients with asthma or COPD.

Another advantage of regadenoson is its method of administration. Regadenoson is administered as a 0.4-mg rapid intravenous bolus, unlike adenosine, which must be dosed by weight and infused over 6 minutes.

In clinical trials, regadenoson was found to be as efficacious as adenosine in assessing the extent of reversible perfusion abnormalities. Additional studies demonstrated that regadenoson was well-tolerated in patients with mild-to-moderate asthma or clinically stable moderate-to-severe COPD.

Regadenoson is contraindicated in patients with second- or third-degree AV block or sinus node dysfunction, unless patients have a functioning artificial pacemaker. The most frequently reported adverse reactions are dyspnea, headache, flushing, chest discomfort, angina or ST segment

(continued on next page)

NOVOSEVEN® RT ROUNDING PROTOCOL

ACTUAL DOSE ORDERED	DOSE DISPENSED TO NEAREST VIAL SIZE	% INCREASE/DECREASE
Less than 1 mg	Dispensed as ordered	
1 mg – 1.4 mg	1 mg	0% ↑ – 29% ↓
1.5 mg – 2.4 mg	2 mg	33% ↑ – 17% ↓
2.5 mg – 3.4 mg	3 mg	20% ↑ – 12% ↓
3.5 mg – 4.4 mg	4 mg	14% ↑ – 9% ↓
4.5 mg – 5.4 mg	5 mg	11% ↑ – 7% ↓
5.5 mg – 6.4 mg	6 mg	9% ↑ – 6% ↓
6.5 mg – 7.4 mg	7 mg	8% ↑ – 5% ↓
7.5 mg – 8.4 mg	8 mg	7% ↑ – 5% ↓
8.5 mg – 9.4 mg	9 mg	6% ↑ – 4% ↓
9.5 mg – 10.4 mg	10 mg	5% ↑ – 4% ↓

Formulary update, *from page 2*
depression, and dizziness. In the Phase III trials comparing regadenoson to adenosine, the overall incidence of adverse reactions and the frequency of rhythm or conduction abnormalities occurred at similar rates.

Currently, regadenoson is slightly less expensive than the large vials of adenosine (Adenoscan®). This is not surprising, since both products are made by the same manufacturer. However, large vials of generic adenosine are expected to become available as early as the Spring of 2009, which could result in a significant cost difference. This would not change the preference for regadenoson in patients with bronchoconstrictive disease, but could make adenosine more cost-effective in most patients. Therefore, the regadenoson was added in the *Formulary*, but it will be reevaluated when the large vials of adenosine become generically available.

Kinrix®, **Pediarix®**, and **Pentacel®** are combination vaccines designed to decrease the number of injections that children receive. In the outpatient setting, where vaccines generally should be administered, these products do provide some advantage (ie, fewer injections). However, in the inpatient setting, it is not possible to stock all versions of all vaccines. Therefore, these products were designated nonformulary and not available.

Diphtheria-tetanus-acellular pertussis (DTaP) is a combination vaccine listed in the *Formulary.* Kinrix®, Pediarix®, and Pentacel® all contain DTaP and inactivated polio vaccine (IPV). Kinrix® only has these 4 components (DTaP + IPV). Pediarix® and Pentacel® also have IPV as the 4th component. Pediarix® has hepatitis B vaccine as its 5th component, and Pentacel® has hemophilus influenza B conjugate vaccine. All of the components of these vaccines are listed in the *Formulary*.

Rotavirus vaccine is an oral live attenuated vaccine for the prevention of the diarrhea associated with rotavirus infections. These infections are the most common cause of gastroenteritis in children and can be serious and even fatal. Thus, rotavirus vaccine is now part of the recommended standard vaccines for children between the ages of 2 and 6 months of age.

Rotarix® is given as a series of 2 doses, while **RotaTeq®** requires 3 doses between the ages of 2 and 6 months. There is more clinical experience with RotaTeq® because it has been on the market longer. There is concern about intussusception with both of these agents because RotaShield® was an oral rotavirus vaccine that was removed from the market in 1999 because of this adverse effect.

Since these are live virus vaccines, they are not recommended in immunocompromised patients. Further, patients who receive the vaccine shed virus after receiving a dose. Therefore, oral rotavirus vaccines were designated nonformulary and not available.

Lidocaine cream (LMX®) and **lidocaine-prilocaine cream** (EMLA®) are topical anesthetics used to decrease the pain associated with injections, venipuncture, or catheter placement.

In June 2008, the P&T Committee deleted EMLA® from the *Formulary* and designated it nonformulary and not available. LMX® was chosen as the only product to anesthetize the skin before venipuncture or catheter insertion in children and adults.

When prescribers have been contacted, they all switch their patients from EMLA® to LMX® (ie, it is the only choice available). Therefore, an automatic interchange of EMLA® orders to LMX® was approved.

Conivaptan is a parenteral vasopressin-receptor antagonist with a labeled indication for the treatment of euvolemic hyponatremia. Conivaptan promotes free water excretion, increases urine output, and decreases urine osmolality through antagonism of both V_{1A} and V_{2A} vasopressin receptors. This aids in normalization of plasma osmolality and serum sodium concentrations.

Hyponatremia is a serious disorder that can lead to various clinical manifestations, including rhabdomyolysis, seizures, respiratory arrest, and death. Therefore, intervention is often needed to correct this condition. Fluid restriction, exogenous sodium, and loop diuretic therapy can be considered for the management of hyponatremia, depending on the fluid status and underlying pathophysiology.

Various studies show that conivaptan increases serum sodium concentrations. Although studies document conivaptan's efficacy for the treatment of euvolemic hyponatremia, trials that compare conivaptan therapy to more commonly used therapies, such as exogenous sodium supplementation, need to be conducted.

Conivaptan is associated with significant injection site reactions (eg, pain and erythema), including phlebitis, in more than 50% of patients. Therefore, peripheral infusion sites should be switched every 24 hours to minimize this risk. Conivaptan is best administered via a central line.

Published studies have suggested that the rise in serum sodium can be rapid (ie, greater than 12 mEq/L over 24 hours), which could put patients at risk for osmotic demyelination syndrome (ie, central pontine myelinosis). Conivaptan is also associated with many drug interactions. It is both a substrate and inhibitor of CYP3A4.

A 4-day regimen of the recommended conivaptan dose (ie, 20 mg IV load followed by 20 mg over 24 hours as a continuous infusion) is estimated to cost the hospital $1200. Although combination hypertonic saline and loop diuretic therapies can be used, fluid restriction is more commonly used to manage euvolemic hyponatremia. Hypertonic saline and loop diuretic therapy cost the hospital and patient a fraction of conivaptan therapy.

Due to the lack of data demonstrating a benefit of conivaptan therapy over other existing therapies, and due to conivaptan's potential adverse effects, drug interactions, and cost, there does not appear to be a reason to use conivaptan for its labeled indication. However, there may be patients in the ICU setting who would benefit from off-labeled use of conivaptan. For example, ICU patients with low sodium values, who need to go to the operating room for a procedure, may benefit from conivaptan therapy when all other measures have failed to sufficiently raise their serum sodium levels. Therefore, conivaptan was added in the *Formulary* in June 2007, but restricted to approval by a clinical pharmacist.

Data from the 1-year experience with this restriction process was reviewed by the P&T Committee to assure that approvals and denials of use were appropriate (see related article on page 1 in this issue of the *Bulletin*). After this review, the P&T Committee continued the current restriction and stipulated that use by a peripheral line will be limited to 12 hours.

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DRUG INFORMATION FORUM

Generic equivalents – Using the Orange Book

The "Orange Book" (properly titled, *Approved Drug Products with Therapeutic Equivalence Evaluations*) is a publication of the FDA commonly used to determine whether prescription products from different manufacturers may be generically interchanged. The term "therapeutic equivalence" refers to bioequivalence between brand and generic products and should not be confused with "therapeutic interchange," which is the process of substituting a product with a different but similar drug (eg, lansoprazole for pantoprazole). In addition to equivalence evaluations, the Orange Book provides lists of all FDA-approved prescription and over-the-counter drugs (some of which may not be currently marketed). As not all generic equivalence matters are intuitive (eg, current HFA albuterol metered-dose inhalers are deemed non-equivalent and should not be interchanged), various practitioners have recently had questions regarding generic substitutions and proper use of the Orange Book.

According to the FDA, drug products are considered to be equivalents and may be interchanged only if they are pharmaceutical equivalents (ie, same active ingredients, dosage form, route of administration, and strength/concentration) and are expected to have the same clinical effect and safety profile when administered under labeled conditions (ie, bioequivalence). Products with "A" codes have no known or suspected bioequivalence problems and may be interchanged. "B" products are those for which bioequivalence has not been proven.

◆

The Orange Book provides lists of all FDA-approved prescription and over-the-counter drugs

If new information raises doubt about previously rated products, the FDA may change their assignment to "B*" (meaning that they should not be interchanged) until the issue is resolved with further bioequivalence testing.

Unfortunately, locating the correct therapeutic equivalence rating is not always a simple task. Products in the Orange Book are listed by the name of the approved application holder who is not always the product manufacturer. If the applicant is not the manufacturer and a corporate relationship (eg, parent and subsidiary) is known, the applicant is listed in the Orange Book and both names are listed on the product labeling. However, if the FDA is unaware of a corporate relationship, only the applicant's name is listed, and it may be difficult to match the listed product with the true manufacturer. Furthermore, many drug products are available through multiple sources, and distributors and repackagers are not identified in the Orange Book. Once the listed applicant is identified, the repackaged/distributed drug can be considered to have the same code and be therapeutically equivalent to the application holder's product. For more information (and to search for generic equivalents), visit the Orange Book online at http://www.fda.gov/cder/orange/default.htm.

by Candice Morris, PharmD