

# Drugs & Therapy

**B • U • L • L • E • T • I • N**

## FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met August 17, 2010. 3 products were added in the *Formulary*, and 1 drug was deleted. 10 products were designated non-formulary and not available. 1 interchange and 2 restrictions were approved.

### ◆ ADDED

**Cefoxitin** (generic)\*

\*Restricted

**Deferasirox**

(Exjade® by Novartis)

**Ritonavir Tablets**

(Norvir® Tablet by Abbott Laboratories)

### ◆ DELETED

**Gemtuzumab** (Mylotarg®)†

†Nonformulary and not available

### ◆ NONFORMULARY AND NOT AVAILABLE

**Denosumab** (Prolia®)

**Dutasteride-Tamsulosin** (Jalyn®)

**Entacapone** (Comtan®)

**Levodopa-Carbidopa-Entacapone** (Stalevo®)

**Memantine ER** (Namenda® XR)

**Meningococcal Vaccine** (Menveo®)

**Nateglinide** (Starlix®)

**Ondansetron Soluble Film** (Zuplenz®)

**Sumatriptan Injection** (Alsuma®)

### ◆ INTERCHANGES

**Memantine IR** (Generic) for **Memantine ER** (Namenda® XR)

(continued on next page)

## PRESCRIBING

### Cation-exchange resins for hyperkalemia: The evidence may leave you in a bind

**T**reatment of hyperkalemia can be a critical issue requiring prompt action. When a rapid correction is necessary, such as a large elevation in serum potassium or an elevation accompanied by electrocardiographic abnormalities, emphasis is first placed upon therapy that produces a quick response.

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**There are limited options for the treatment of hyperkalemia. Consideration of the likely reduction in potassium level produced by an intervention, the time needed to achieve the desired outcome, and the potential risks of a given therapy are all critical in successful treatment.**

Intravenous calcium is often employed to protect the heart against arrhythmias. Insulin and dextrose infusions are given to promote intracellular potassium redistribution.

After performing temporizing measures, the focus shifts to correction of the underlying hyperkalemia. For those patients with dialysis access, this option offers effective therapy. Alternatively, loop diuretics may be useful in patients with adequate renal function.

Oral cation-exchange resins, such as sodium polystyrene sulfonate (SPS), are another means of correcting the underlying potassium elevation. Given their frequent use for an indication that is often urgent in nature, it may be expected that exchange resins

work quickly to produce a significant lowering in serum potassium with little potential for adverse effects. However, the evidence for rapid potassium-lowering effect is lacking.

Furthermore, reports describing intestinal injury associated with sodium polystyrene sulfonate suspension in sorbitol and recent labeling changes for Kayexalate® powder for suspension advising against the concomitant use of sorbitol have raised concern for the product's safety.<sup>1</sup>

Having been available as a treatment for hyperkalemia for more than 50 years, SPS has achieved a relative permanence in drug therapy that is uncommon. Kayexalate® powder for suspension was originally approved by the Food and Drug Administration (FDA) in 1958, 4 years prior to the passage of the Kefauver-Harris amendment that required drugs be proven effective in addition to being safe for use under the conditions described in their label.<sup>2</sup> After the passage of Kefauver-Harris, the FDA contracted with the National Academy of Sciences to evaluate the efficacy of drugs approved prior to 1962. Naturally, this evaluation required examination of the available clinical evidence, which was limited to several small case series and a clinical study reported by Scherr and colleagues in 1961. In this study, the investigators reported a significant lowering of plasma potassium in 23 of 30 patients by a minimum of 0.4 mEq/L in the first 24 hours. Treatment regimens ranged from 20 to 60 grams daily of SPS suspended in water administered in divided doses. The most significant lowering of plasma potassium levels by exchange resin occurred over the course of 2 or more days.<sup>3</sup> The authors reported the therapy was effective, generally well-tolerated, and occasion-

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◆ **CRITERIA-FOR-USE CHANGES**

**Cabazitaxel** (Jevtana®)‡

‡Nonformulary drug: must be ordered on a Chemotherapy Order Form

**Dexmedetomidine** (Precedex®)§

§OR uses for children approved

**Cefoxitin** is a second-generation cephalosporin that was re-added in the *Formulary* but restricted to use in the treatment of rapid-growing mycobacteria. Its use requires approval by Infectious Diseases or the Division of Mycobacteriology.

In April 2008, cefotetan was designated the preferred second-generation cephalosporin in the *Formulary*. At that time, cefoxitin was designated nonformulary and not available and was interchanged to cefotetan. However, exceptions were made to this policy for rapid growing mycobacteria.

Cefoxitin is recommended for rapid-growing mycobacteria by the American Thoracic Society Guidelines on the management of nontuberculous mycobacterium. Cefoxitin is several dilutions more potent than cefotetan against rapid-growing mycobacteria.

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**Deferasirox** is a once-daily, oral, iron-chelating agent with a labeled indication to treat chronic iron overload from frequent blood transfusions due to anemias or from myeloproliferative disorders. Deferasirox is an alternative to deferoxamine (Desferal®), which is currently used as the standard treatment for chronic iron overload. Deferoxamine is administered parenterally.

Deferasirox is under investigation for the treatment of mucormycosis in combination with liposomal amphotericin B. Deferoxamine acts as a siderophore, binding iron that is then internalized by the fungus and facilitating growth. In contrast, deferasirox does not foster but instead inhibits fungal growth. A double-blinded, randomized, placebo-controlled, phase II safety/exploratory efficacy study of adjunctive deferasirox therapy for mucormycosis is ongoing (the DEFEAT Mucor study).

Clinical trials for iron chelation with deferasirox were noninferiority trials with deferoxamine. Subgroup analyses suggest that when administered at the FDA approved dose of 20 mg/kg, deferasirox was noninferior to deferoxamine. Adequately powered studies are needed to prove these iron chelators are equally

effective since the published data are limited. Thus, deferasirox should not routinely replace deferoxamine.

Use of deferasirox in patients with advanced kidney and liver dysfunction, high-risk myelodysplastic syndromes or advanced malignancies, and platelet counts less than  $50 \times 10^9/L$  is contraindicated. Monitoring serum creatinine and liver transaminases is vital, and caution must be used in patients who have a history of gastrointestinal bleeds since fatalities have occurred. The likelihood of developing ocular and auditory disturbances is similar between deferasirox and deferoxamine.

There is insufficient evidence to use deferasirox as an anti-infective agent at this point; however, if patients are iron-overloaded and have mucormycosis infections, it provides an alternative to deferoxamine.

**Ritonavir tablets** were added in the *Formulary* to provide continuity of care for patients with HIV admitted taking this dosage form. Ritonavir capsules have been listed in the *Formulary*. Ritonavir capsules must be refrigerated, which can be inconvenient for patients. Ritonavir tablets are heat-stable.

Similar to the capsule, each ritonavir tablet contains 100 mg of active product. However, the tablet formulation is absorbed differently, leading to a 26% increase in serum concentrations when compared to the capsule. The main concern with this difference is the potential for gastrointestinal adverse events.

Most clinicians feel the differences in bioavailabilities are minor, considering ritonavir is used as a low dose in combination with other protease inhibitors. An interchange policy with the 2 formulations was considered, but due to the potential for discharge on the wrong formulation, the tablets were added in the *Formulary*.

**Gemtuzumab** ozogamicin is a monoclonal antibody that binds to the CD33 antigen, which is expressed on the surface of leukemic myeloblasts and immature normal cells of myelomonocytic lineage. Gemtuzumab has a labeled indication for the treatment of acute myeloid leukemia (AML).

Gemtuzumab was approved by the FDA in 2000 by an accelerated approval process based on surrogate endpoints. Drugs that address an unmet medical need are eligible for accelerated approval.

A confirmatory, post-approval study designed to study the effect of gemtuzumab on survival in the labeled population was stopped early when no improvement in clinical benefit was observed. Further, a greater number of deaths occurred in the gemtuzumab-treated patients compared with chemotherapy alone. Based on the results of

this study, Mylotarg® was withdrawn from the market and is available only to patients who are currently receiving the drug [in order to complete therapy].

**Denosumab** is a monoclonal antibody against the receptor that activates osteoclasts. Binding to this receptor decreases bone loss by decreasing bone breakdown. Denosumab has a labeled indication for the treatment of postmenopausal women with osteoporosis at high risk for fracture.

Denosumab is administered subcutaneously by a healthcare provider every 6 months. Since this drug is administered infrequently and its cost is not considered in fixed reimbursement schemes, denosumab was designated nonformulary and not available for inpatient use.

**Jalyn®** is a fixed combination of dutasteride (Avodart®) and tamsulosin (Flomax® and now generics) with a labeled indication for the treatment of symptomatic benign prostatic hyperplasia (BPH) in patients with an enlarged prostate. Although tamsulosin is listed in the *Formulary*, dutasteride is nonformulary and not available. Jalyn® was designated nonformulary and not available.

**Entacapone** was reviewed because of high-volume nonformulary use (ie, 3 patients a month or higher in some months). Entacapone has a labeled indication as adjunctive therapy to levodopa-carbidopa to treat patients with idiopathic Parkinson's disease who experience the signs and symptoms of end-of-dose "wearing-off."

Entacapone belongs to the class of catechol-O-methyltransferase (COMT) inhibitors that inhibit the metabolism of catecholamines. Entacapone is ineffective when given alone, but it may prolong and potentiate the levodopa effect in the central nervous system when given concomitantly. Entacapone should be co-administered with each levodopa-carbidopa dose. A dose reduction in levodopa is sometimes required to reduce dose-related adverse effects (eg, dyskinesia, nausea). Acute disruption in the entacapone dose could lead to the emergence of signs and symptoms of Parkinson's disease. If the treatment of entacapone needs to be discontinued, patients should be monitored closely and tapered off.

Current studies of entacapone to treat patients with motor fluctuations who are experiencing end-of-dose "wearing-off" periods fail to show clinically significant improvements in Unified Parkinson Disease Rating Scale motor scores. However, these studies have numerous limitations,

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**Formulary update**, from page 2 including the effectiveness of the rating scale and the duration of Parkinson's disease in the patients studied. Further studies are necessary to analyze the effectiveness of entacapone on patients with Parkinson's disease longer than 5-10 years.

In preclinical studies, dyskinesia, hyperkinesia, nausea, urine discoloration, diarrhea, and abdominal pain were not only the most common adverse events (greater than 5%) observed in the entacapone group, but were also not seen in equivalent frequencies among the placebo group. Rhabdomyolysis and fibrotic complications are rare but have been reported with entacapone use. Entacapone should not be combined with any non-selective monoamine oxidase inhibitors due to an increased risk of catecholamine-related adverse effects. Also, entacapone may increase the concentration of drugs metabolized by COMT and potentiate their adverse effects.

Both entacapone (Comtan<sup>®</sup>) and the combination product entacapone-levodopa-carbidopa (**Stalevo<sup>®</sup>**) are available as brands only. Levodopa-carbidopa is available as a generic and is 1/3 the cost.

There are limited data showing benefit for entacapone. The addition of entacapone to levodopa-carbidopa treatment can increase pill burden, cost, or both. On August 20, 2010, the FDA released data that suggest an increased cardiovascular risk in patients taking levodopa, carbidopa, and entacapone. Therefore, entacapone (Comtan<sup>®</sup> and Stalevo<sup>®</sup>) was designated nonformulary and not available. Patients can use their own medication since acute disruption in the entacapone dose could lead to the emergence of signs and symptoms of Parkinson's disease.

**Namenda<sup>®</sup> XR** is a once-daily, extended-release dosage form of **memantine** with a labeled indication for the treatment of moderate to severe dementia of the Alzheimer's type.

**Immediate-release (IR) memantine** is listed in the *Formulary*. A generic version of memantine IR has recently been approved, and after an exclusivity period, memantine IR should be available from multiple vendors. Thus, Namenda<sup>®</sup> XR will ultimately be much more expensive than the IR.

Namenda<sup>®</sup> XR was designated nonformulary and not available and will be automatically interchanged to memantine IR. Namenda<sup>®</sup> XR 28 mg

and 14 mg daily will be interchanged to memantine 10 mg BID or 5 mg BID respectively. This interchange is recommended in the official labeling for Namenda<sup>®</sup> XR.

Menactra<sup>®</sup> is the conjugate meningococcal vaccine listed in the *Formulary*. **Menveo<sup>®</sup>** is a new formulation approved by the FDA in February 2010. Based on seroresponse, Menveo<sup>®</sup> was shown to provide higher bactericidal activity based on serum response to key capsular components. The clinical relevance of higher serum titers is unknown.

The Advisory Committee on Immunization Practices recommended either Menactra<sup>®</sup> or Menveo<sup>®</sup> for meningococcal vaccination. Neither agent is preferred over the other. Therefore, Menveo<sup>®</sup> was designated nonformulary and not available and Menactra<sup>®</sup> remains the preferred choice.

**Nateglinide** is a member of the meglitinide class of hypoglycemic agents used for the treatment of type 2 diabetes. Nateglinide stimulates insulin secretion from functional pancreatic beta cells in a glucose-dependent manner by binding to ATP-sensitive potassium channels. Nateglinide is a D-phenylalanine derivative, which distinguishes it from the sulfonylurea class; however, both medications share a similar mechanism of action to induce pancreatic insulin secretion.

Nateglinide has a labeled indication for adjunctive use with diet and exercise to improve glycemic control in adults with type 2 diabetes. It may be used as monotherapy, or in combination with metformin and thiazolidinediones. Nateglinide primarily lowers postprandial blood glucose.

The recommended starting and maintenance dose is 120 mg 3 times daily, taken 1 to 30 minutes before meals. If the patient skips a meal, the dose of nateglinide should be held to reduce the incidence of hypoglycemia. Patients with renal and hepatic insufficiency should be monitored for increased hypoglycemic effects, but no dosing adjustment is required.

Efficacy studies show nateglinide is more effective at reducing postprandial glucose release and causes less insulin secretion compared to glyburide; however, the overall mealtime glucose control is similar between these medications. Data suggest nateglinide is less effective at reducing Hb<sub>A1c</sub> than sulfonylureas, metformin, and thiazolidinediones.

The most commonly reported adverse event is upper respiratory tract

infections. Other reported adverse effects include back pain, flu-like symptoms, dizziness, arthropathy, diarrhea, bronchitis, coughing, and hypoglycemia. Nateglinide is a major substrate of CYP2C9 (70%) and CYP3A4 (30%) and a weak inhibitor of CYP2C9. Thus it has potential to cause drug-drug interactions.

Nateglinide was designated nonformulary and not available. The American Diabetes Association (ADA) guidelines support the use of insulin over oral agents for inpatient therapy. Patients will be permitted to use their own supply from home, if ordered.

**Zuplenz<sup>®</sup>** is a soluble film dosage form of the antiemetic ondansetron. Since orally disintegrating tablets are listed in the *Formulary*, Zuplenz<sup>®</sup> was designated nonformulary and not available.

**Cabazitaxel** is a microtubule stabilizer with anti-tumor activity. It has a labeled indication in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

Cabazitaxel was added in the Chemotherapy Policy (ie, requiring a chemotherapy order form). It was not considered for addition in the *Formulary* at this time.

**Dexmedetomidine** is a relatively selective alpha<sub>2</sub>-adrenoceptor agonist with centrally mediated sympatholytic, sedative, and analgesic effects. Its pharmacology has always been intriguing; however, there are few data suggesting that outcomes, like time to extubation, are better than with other agents used for general sedation in a critical care setting.

Most of the evidence for dexmedetomidine was limited to expert opinion, case series, case reports, and [rarely] observational studies. The only controlled trials compared dexmedetomidine to placebo. For many indications, there are less expensive alternatives.

Dexmedetomidine was approved for single dose uses in the Operating Room (OR) when there are no other alternatives. Expanded use in children include treatment of emergence delirium; as a premedication for patients with paradoxical reactions to other agents; as a nasal premedication for patients refusing oral midazolam; and, as a premedication for patients with extreme anxiety or neurobehavioral disorders.

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**EDITOR,  
DRUGS & THERAPY BULLETIN**

Randy C. Hatton, PharmD

**DIRECTOR,  
PHARMACY SERVICES**

Alan Knudsen, MS, RPh

**CHAIRMAN,  
PHARMACY & THERAPEUTICS  
COMMITTEE**

Ricardo Gonzalez-Rothi, MD

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*Prescribing, from page 1*

ally produced constipation, which was easily remedied with enemas or cathartics.

The ability of SPS powder to cause severe constipation and a desire to speed its delivery to the colon led to the development of SPS suspension in sorbitol, the formulation most often employed in current practice.<sup>2</sup> The evidence of the efficacy of SPS suspended in sorbitol is equally sparse but does tend to support the need for an extended duration of therapy to realize a significant therapeutic effect. One study reported an average decrease of 1.4 mEq/L in serum potassium in 5 patients over a 5-day period in patients receiving varying doses.<sup>4</sup> This result and that reported by Scherr and colleagues demonstrate the extended time and repeated dosing likely necessary to achieve a significant therapeutic effect. The official labeling of Kayexalate® reinforces this fact with the statement that significant lowering of serum potassium may require hours to days when used alone.

Safety concerns surrounding the use of SPS suspension in sorbitol are equally perplexing. Case reports are available in the literature describing colonic necrosis due to oral administration of SPS with and without

concomitant use of sorbitol. Similar adverse events have been reported with the use of SPS in sorbitol enemas. In response to adverse events related to use of SPS suspended in sorbitol, the recommendation for the use of sorbitol with SPS was removed from the approved labeling of the powdered formulation. This appears to be contradictory when a formulation of SPS in sorbitol remains on the market. However, manufacturers of the SPS suspension were permitted to continue to market the product based on evidence provided to the FDA in 2006 that the reports of adverse gastrointestinal events occurred with the use of SPS suspended in 70% sorbitol and that the largest manufacturer of the premixed suspension, whose product contained 33% sorbitol, had, at the time, received no reports of adverse events despite millions of doses used annually.<sup>2</sup> Currently marketed premixed suspensions of SPS all utilize a 33% sorbitol formulation.

From case reports in the literature, it is difficult to discern the exact formulation of SPS suspension involved in the adverse events. Despite the likelihood that some cases of bowel necrosis involve the SPS in 33% sorbitol formulation, it appears to be a rare complication whose risk of occurrence

can be minimized by avoiding its use in patients with decreased bowel motility, whether related to a medical disorder or drug-related, or in the post-operative period.<sup>5</sup> Additionally, the official labeling of the pre-made suspension includes the use of a non-sodium-containing cleansing enema before and after use of the product when administered as a rectal suspension to help promote removal of the resin from the colon.

There are limited options for the treatment of hyperkalemia. Consideration of the likely reduction in potassium level produced by an intervention, the time needed to achieve the desired outcome, and the potential risks of a given therapy are all critical in successful treatment.

*By Joseph Shultz, PharmD*

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