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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met April 21, 2009. 4 drugs were added in the *Formulary,* while 1 was deleted and will be interchanged to a formulary alternative. 2 drugs were designated nonformulary and not available. Restriction criteria were changed for 3 drugs, and 1 dose standardization was approved.

◆ ADDED

Capsaicin topical cream (Generics)

Omega-3 Fatty Acids (Lovaza® by GlaxoSmithKline)

Rufinamide (Banzel® by Eisai)

Sevelamer carbonate (Renvela® by Genzyme)

◆ DELETED

Sevelamer hydrochloride (Renagel® by Genzyme)*

**Nonformulary and not available. Interchanged*

◆ NONFORMULARY AND NOT AVAILABLE

Ferrous gluconate (Generics)

Zolpidem sublingual tablet (Edluar® by Orexo)

◆ INTERCHANGES

Sevelamer carbonate for **Sevelamer hydrochloride**

◆ CRITERIA-FOR-USE CHANGES

Enoxaparin (Lovenox® by Sanofi-Aventis)†

†Doses greater than 40 mg rounded to nearest 10-mg increment

Temozolomide for injection (Temodar® by Schering)‡

‡Must be ordered using a Chemotherapy Order Form

(continued on next page)

POLICIES AND PROCEDURES

Change to vaccination policy

The Medical Executive Committee has expanded the policy regarding pneumococcal and influenza vaccination to align with new Centers for Medicare and Medicaid Services core measure directives for pneumonia. Effective April 1, 2009, the revised core measures mandate that all pneumonia patients meeting designated criteria are screened for pneumococcal and influenza vaccine status and receive the vaccines prior to discharge, if indicated. In addition to the vaccination requirements, other components included in the core measure are timely obtainment of blood cultures, smoking cessation counseling, and appropriate antibiotic selection and timing.

Key changes to the policy are house-wide pneumococcal and influenza vaccination (regardless of admitting diagnosis) and a nursing-physician protocol. A *Pneumonia & Flu Vaccination Screening Form* will be placed in each admission packet.

Inclusion criteria to receive the pneumococcal vaccine are age greater than or equal to 65 years; tobacco use; and asplenia. Additionally, the pneumococcal vaccine is indicated for patients older than 65 years who received the vaccine within the previous 5 years and were less than 65 years at the time of prior vaccination. The influenza vaccine is indicated for all patients hospitalized during "flu season" (October through March) who are at least 50 years old; have conditions that can compromise respiratory function or increase risk of aspiration (eg, cognitive dysfunction, seizure disorders); are pregnant women in the 2nd-3rd trimester; are household contacts of young children; and are healthcare providers. Inclusion criteria common to both vaccines are chronic heart, lung, renal, hepatic, or metabolic disease (eg, emphysema, diabetes, cirrhosis, sickle cell disease); and immunocompromised state.

The key changes to the policy are house-wide pneumococcal and influenza vaccination (regardless of admitting diagnosis) and a nursing-physician protocol. A *Pneumonia & Flu Vaccination Screening Form* will be placed in each admission packet. A nurse will assess each patient's vaccination history for both vaccines upon admission to medical/surgical units and upon transfer or discharge from intensive care units. If the patient has been vaccinated, the status will be documented in the chart; if the patient has not been vaccinated (or the vaccination history cannot be verified), the nurse will complete the *Vaccination Risk Assessment.* The physician will then review the screening form and either order or decline the vaccine. If the vaccine is declined, the reason for not administering must be provided.

This process replaces the current physician-approved, pharmacy-directed protocol which is focused solely on patients with an admitting diagnosis of pneumonia. After a successful 1-month pilot on a medical/surgical unit, the new process was implemented house-wide at the beginning of May.

By Candice T. Morris, PharmD

INSIDE THIS ISSUE

Formulary update, *from page 1*

◆ CRITERIA-FOR-USE CHANGES (cont.)

Thioridazine (Generics)§

§Restricted: Concomitant use with QT-prolonging agents prohibited

Ranolazine (Ranexa® by CV Therapeutics)¶

¶Concomitant use with moderate CYP 3A4 inhibitors or QT-prolonging agents no longer contraindicated

Capsaicin is used over-the-counter for multiple conditions, including diabetic neuropathy, mild to moderate pain, rheumatoid and osteoarthritis, and postherpetic neuralgia. Although capsaicin has shown limited efficacy in the treatment of chronic musculoskeletal or neuropathic pain, it may be useful as an adjunct or sole therapy for a small number of patients who are unresponsive to, or intolerant of, other treatments. Results from a meta-analysis of 16 randomized, controlled trials demonstrate that capsaicin is significantly better than placebo for the treatment of both neuropathic and musculoskeletal pain, but data were insufficient to draw any conclusions concerning the relative efficacy for alternative drugs or doses.

Topical capsaicin therapy has several advantages and disadvantages. There are currently no known drug interactions, so patients unable to take other analgesic products due to interactions would be possible candidates for this therapy. The topical route may also be preferred in patients intolerant of oral analgesics. However, the frequency of administration (3-4 times/day), time to pain relief (2-6 weeks), and relatively common incidence of local adverse effects (burning, stinging, and tingling) may detract from the pain reduction found in clinical trials. To reduce the risk of adverse effects, nurses should wear gloves when applying capsaicin cream. Patients and nurses should avoid touching the area of application then touching mucous membranes (eg, eyes). Because evidence suggests topical capsaicin may be a suitable option for neuropathic or musculoskeletal pain for patients who fail other first- and second-line treatments, it was added in the *Formulary*.

Lovaza® is the first **omega-3 fatty acid** product to be approved as a prescription drug by the FDA. It was formerly known as Omacor®, but the trade name was changed because of medication errors associated with sound-alike drugs (eg, Amicar®). Lovaza® has a labeled indication as an adjunct to diet in patients with very high triglyceride (TG) levels (≥ 500 mg/dL). While not indicated in the labeling, there is substantial literature on its off-label use for TG-lowering effects in patients with high triglyceride levels (200-499 mg/dL).

To date there are 10 prospective, randomized trials that have examined the effect of Lovaza® 4 grams daily on TG and low-density lipoprotein cholesterol (LDL-C) levels in patients with elevated TG levels. Four of these have examined Lovaza® as monotherapy and demonstrated serum reductions in TGs by an average of 28% in the setting of high triglycerides (200-499 mg/dL) and by as much as 45% when administered chronically in the setting of very high triglyceride levels (≥ 500 mg/dL). Three of these trials have administered Lovaza® to patients on background simvastatin. On average, Lovaza® has decreased serum TGs between 28 and 35% without attenuating simvastatin's beneficial effects on LDL-C. One trial has compared Lovaza® to an active treatment (ie, gemfibrozil) and found that both agents significantly reduce serum TG levels from baseline. There was no significant difference found between agents. Thus, there is no evidence that Lovaza® is better or worse than alternative agents.

Lovaza® is usually well-tolerated. The most common adverse effects are limited primarily to the gastrointestinal tract (eg, eructation, dyspepsia, taste-perversion/fishy taste). When Lovaza® is given as monotherapy, it can result in a significant rise in LDL-C; however, this elevation appears not to occur when Lovaza® is given concurrently with simvastatin therapy. It is recommended that patients receiving Lovaza® have their LDL-C levels periodically monitored.

Although there are fish oil dietary supplements, Lovaza® is a unique prescription drug and there is no therapeutic alternative to continue in patients who are admitted to the hospital and take this medication chronically at home. Despite a higher per-capsule cost compared to most other formulary agents, the small number of patients for which it is ordered should not adversely affect hospital expenditures. Therefore, Lovaza® was added in the *Formulary*.

Rufinamide is a new antiepileptic drug (AED) added in the *Formulary* as an alternative adjunctive therapy for seizures associated with Lennox-Gastaut syndrome (LGS) — a form of pediatric epilepsy that usually begins in early childhood. It has been estimated that LGS affects up to 4% of all children with epilepsy and significantly contributes to childhood morbidity. The syndrome is characterized by multiple seizure types that occur at a high daily frequency and impaired mental development. Valproic acid is usually recommended as the first-line treatment with lamotrigine, felbamate, and/or topiramate as adjunctive therapies. However, it is not uncommon for these patients to have poor seizure control even when they are receiving appropriate polytherapy.

Rufinamide has a labeled indication for adjunctive treatment of seizures associated with LGS in children 4 years and older and adults. The exact mechanism of action of rufinamide is unknown, but it is believed to limit excessive firing of sodium-dependent action potentials resulting in membrane-stabilizing effects.

For adults, the recommended starting dose of rufinamide is 400–800 mg/day; the dose is titrated until a maximum daily dose of 3200 mg/day is reached. For children 4 years and older, the starting dose of 10 mg/kg/day is titrated to a target dose of 45 mg/kg/day or 3200 mg/day (whichever is less). No dosage adjustment is required in patients with renal impairment. Rufinamide should be avoided in patients with severe hepatic impairment.

Rufinamide was approved for this indication based on the results from 1 randomized controlled trial of patients aged 4 and older. In this study, rufinamide or placebo was added to the patient's baseline regimen. It was found that the addition of rufinamide resulted in significantly greater reductions in seizure frequency and severity relative to baseline when compared to placebo. Additional studies have shown that rufinamide may also be effective as an adjunctive therapy for the treatment of adolescents and adults with partial-onset seizures.

The use of rufinamide is contraindicated in patients with Familial Short QT Syndrome. The most common CNS reactions observed with rufinamide treatment were somnolence, fatigue, dizziness, ataxia, and gait disturbance.

The *Formulary* currently contains all of the AEDs most commonly used for LGS – valproic acid, lamotrigine, topiramate, and felbamate. Although the cost of rufinamide is high (approximately $20 per patient day; based on the maximum dose of 3200 mg/day), it should not significantly affect overall costs due to low expected usage. Rufinamide is not expected to replace other currently available AEDs and will likely remain a third-line adjunctive therapy due to limited experience with this new drug. Most patients will

(continued on next page)

Formulary update, *from page 2*
likely receive the medication as a continuation of home therapy; however, some patients may be started on the drug in the inpatient seizure unit in severe cases.

The manufacturer of **Renagel® (sevelamer hydrochloride)**, Genzyme, has announced plans to transition all patients to **Renvela® (sevelamer carbonate)** by September 30, 2009. (Renagel® will no longer be available after this date.) In preparation for this nationwide transition, Renvela® was added in the *Formulary* and Renagel® was deleted from the *Formulary* and designated nonformulary and not available. Renvela® will be automatically interchanged for Renagel®, using a mg-per-mg conversion (ie, 800 mg of Renvela® for 800 mg of Renagel®).

Renvela® has been available since March 2008. Like Renagel®, it is a calcium-free, metal-free, non-absorbed treatment approved for the control of serum phosphorus in patients with chronic kidney disease on dialysis. In a clinical study comparing tablet formulations of Renvela® to Renagel®, both drugs controlled serum phosphorus within Kidney Disease Outcome Quality Initiative (KDOQI) recommended ranges. Renvela® maintained serum phosphorus at a mean level of 4.6 mg/dL. Patients treated with Renvela®, however, were more likely to achieve bicarbonate levels within the recommended KDOQI ranges and had a lower overall incidence of gastrointestinal adverse events.

Because **ferrous gluconate** has been a frequently used nonformulary agent, it was compared with ferrous sulfate (the oral iron supplementation agent listed in the *Formulary*) to determine if there is a need for both. Both ferrous sulfate and ferrous gluconate are well absorbed but differ by their elemental iron content. The hydrated ferrous sulfate formulation contains 20% iron and the dried form has 32% elemental iron. Ferrous gluconate contains only 12% elemental iron available for absorption. For example, at a dose of 300 mg of hydrated ferrous sulfate, 60 mg of elemental iron is present. However, a 325-mg dose of ferrous gluconate is equivalent to only 36 mg of elemental iron. Therefore, the dose of ferrous gluconate would need to be doubled to equal the amount of elemental iron in a 300-mg ferrous sulfate tablet.

The misconception that ferrous gluconate has fewer adverse effects compared with ferrous sulfate is based on nonequivalent amounts of elemental iron. If similar amounts of elemental iron are compared, the adverse effects are expected to be the same. Therefore, ferrous gluconate was designated nonformulary and not available.

A sublingual formulation of **zolpidem**, **Edluar®**, was approved in March 2009. Like other zolpidem formulations, Edluar® is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. The sublingual tablet is bioequivalent to oral tablets with respect to Cmax and AUC. Because this formulation appears to offer no therapeutic benefit over currently available agents, the zolpidem sublingual tablet was designated nonformulary and not available.

Enoxaparin is available in pre-filled syringes in varying doses (eg, 30 mg; 40 mg; 60 mg; 80 mg; 100 mg). Dose customization is necessary for doses other than those available as a standard syringe. Currently, there is no protocol to address non-standard doses. The variability in dose-rounding and administration (syringes are not sufficiently graduated to allow dose customization) poses a significant risk to medication safety.

Therefore, all enoxaparin doses greater than 40 mg will now be standardized and rounded to the "nearest 10 mg" (ie, 76 mg rounded to 80 mg). The minimum standard dose of 40 mg prevents inadvertent dose rounding in pediatric patients in whom seemingly small dosage changes could lead to significant therapeutic differences.

Temozolomide is an alkylating agent with labeled indications for the treatment of adult patients with glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment and for refractory anaplastic astrocytoma. Temozolomide has been available as an oral capsule since 1999; an injectable formulation for administration as an intravenous infusion was approved in February 2009.

Temozolomide is included in the *Chemotherapy Policy*, which mandates that all orders written for chemotherapy agents must be written on the P&T Committee-approved *Chemotherapy Order Form* and will receive special handling and review by Pharmacy and Nursing Departments. This policy applies to both oral and injectable chemotherapy agents prescribed for oncology and non-oncology indications. Temozolomide capsules are included in the *Formulary*; temozolamide for injection will remain nonformulary until it is formally reviewed for addition.

Thioridazine is a conventional antipsychotic approved by the FDA in 1959. Of the conventional antipsychotic agents, thioridazine has the most restrictive labeling. It has been shown to prolong the QT interval in a dose-related manner, and drugs like thioridazine have been associated with drug-induced torsade de pointes arrhythmias and sudden death. Therefore, thioridazine use is contraindicated in combination with other drugs that are known to prolong the QT interval and in patients with congenital long QT syndrome or a history of cardiac arrhythmias. Additionally, the labeling states that thioridazine should be reserved for use in the treatment of schizophrenic patients who fail to show an acceptable response to adequate courses of treatment with other antipsychotic drugs.

Although thioridazine use is low and it poses significant safety concerns, it will remain in the *Formulary* to preserve continuity of care for patients who have been controlled on thioridazine for years. However, in order to reduce the risks associated with thioridazine, its use is restricted to conform to its labeling (ie, concomitant use with QT-prolonging agents is prohibited). Since the warnings for thioridazine are very similar to those previously listed for ranolazine (Ranexa®), it has been recommended that the use of thioridazine be restricted by a similar mechanism. Prescribers will be required to select an alternative therapy and patient profiles will be monitored daily.

The FDA has recently approved new labeling for **ranolazine** as an initial therapeutic option for the treatment of patients with chronic angina. With the revised labeling, the FDA removed contraindications for use with moderate cytochrome P450 (CYP) 3A inhibitors (eg, diltiazem, verapamil, erythromycin, fluconazole) and QT-prolonging drugs. However, the maximum dose of ranolazine should not exceed 500 mg twice daily when used with moderate CYP 3A inhibitors. Additionally, the effects of high doses (> 1000 mg twice daily) in combination with QT-prolonging drugs are not known.

The expanded labeling for ranolazine is based on safety observations from a large acute coronary syndrome (ACS) outcomes trial, MERLIN-TIMI 36 (N = 6560). Although the results of the trial were not statistically significant for the primary endpoint (treatment of ACS), the additional safety information obtained helped lead to the broader indication and revised labeling. Ranolazine is still contraindicated in patients taking strong inhibitors of CYP3A (eg, ketoconazole, itraconazole, clarithromycin), taking inducers of CYP3A (eg, rifampin, phenobarbital, phenytoin), and with clinically significant hepatic impairment. In light of these revisions to the product labeling, the use of ranolazine with moderate CYP 3A inhibitors or QT-prolonging drugs is no longer designated as contraindicated.

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POLICIES AND PROCEDURES

Conflicts of interest — "Perception is reality"

The term "conflict of interest" has been defined as a set of conditions in which professional judgment concerning a primary interest (eg, institutional responsibility) may be unduly influenced by a secondary interest (eg, financial gain). Conflicts of interest can arise from financial ties between physicians and industry, including honorariums for speaking or writing about a company's product.

Since the early 1990s, numerous studies and position statements have emphasized the importance of maintaining ethical relationships between industry and the medical profession. However, there are still concerns that industry relations continue to impact clinical judgment. Recent studies have demonstrated industry's influence on physician objectivity and behavior, particularly on prescribing practices, formulary choices, and assessment of medical information.

Identifying potential conflicts of interest has been proven to be a very interesting matter; this is largely due to the fact that the occurrence of conflicts of interest is determined not by one's own standards but by the perceptions of others. Since perception greatly drives conflict of interest, helpful questions for gauging whether an industry relationship is ethically appropriate include: 1) *What would my patients think about this arrangement?* 2) *What would my colleagues think?* 3) *What would I think if my own physician accepted this offer?*

Perhaps more important than avoiding conflicts of interest in individual decisions is the need to preserve the credibility of the Pharmacy and Therapeutic (P&T) Committee's deliberations and decisions (which affect medication use for the entire institution). In order to help ensure that the decision-making process is based solely on the best available scientific evidence, the P&T Committee has revised its *Disclosure and Conflict of Interest Policy.* Under the revised policy, all P&T Committee members will disclose annually all relationships that they or their family members have with industry and recuse themselves from any final deliberations when a potential conflict of interest could be perceived by others. All medical staff or pharmacists who request action on a formulary topic or drug use policy must disclose any potential conflict of interest and not participate in any final deliberations by the P&T Committee. Additionally, anyone preparing reviews or evaluations that the P&T Committee will use as a resource to make decisions must disclose any industrial relationships.

P&T Committee members, medical staff members with issues before the Committee, and staffers may have relationships with industry yet serve as P&T Committee experts. They may provide background on an issue in consideration (eg, addition of the drug in the *Formulary*). This expertise will be considered; however, the expert will not participate in the final deliberations or voting on a motion before the Committee. This allows input from those with expertise; yet it maintains the integrity of the process.

It is imperative that serving the public interest remain the primary focus of all Committee activities and that any circumstances that might be viewed as a conflict of interest in serving that trust be avoided.

By Candice T. Morris, PharmD