Volume 24, Number 5

Shands at the University of Florida

May 2010

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met April 20, 2010. 4 products were added in the *Formulary,* and 12 products were deleted. 17 products were designated nonformulary and not available. 4 interchanges were approved.

◆ ADDED

Cholecalciferol Liquid 400 units/mL (D-Vi-Sol® by Mead Johnson)*

**Vitamin D_3*

Cholecalciferol Tablets 1000 units (Generic)*

Ergocalciferol Capsules 50,000 units (Generic)†

†Vitamin D_2

Leflunomide (eg, Arava® by Sanofi-Aventis)

◆ DELETED

Benzocaine Gel (HurriCaine® Topical Anesthetic Gel by Beutlich Pharmaceuticals)‡

‡Nonformulary and not available

Cimetidine (Generic)‡

Dipivefrin Ophthalmic Solution (Propine® by Allergan)‡

Ergocalciferol Injection (Calciferol® by Schwartz Pharma)†‡

Ergocalciferol Oral Suspension 1000 units/mL (Compounded)†‡

Ethiodized Oil (Ethyol® by Savage Laboratories)‡

Ganciclovir Capsules (eg, Cytovene® by Roche)‡

Ganciclovir Suspension (Compounded)‡

Pancrelipase Powder (Viokase® Powder by Axcan Pharma)‡

(continued on next page)

MEDICATION SAFETY

The importance of accurate drug allergy information

When a patient is truly allergic to a medication, it is extremely important that this information be listed in the patient's chart. This information needs to be in the hospital's computer systems for appropriate electronic screening for these allergies. This is necessary to minimize the risks of unnecessary adverse drug reactions.

...information needs to be in the hospital's computer systems for appropriate electronic screening for allergies. This is necessary to minimize the risks of unnecessary adverse drug reactions.

It is equally important to remove inaccurate allergy information from the patient's chart. Patients often report previous adverse drug reactions to a drug that are not allergies. These reactions may not prevent re-administration of that drug, despite their perceived "allergy." By avoiding a medication that does not need to be avoided, a patient may unnecessarily be exposed to a less effective, more expensive, or more risky agent.

Taking a thorough history of a patient's past allergic reactions is a challenge. Patients often do not understand the difference between an allergy and adverse effects. Common adverse effects may be falsely recorded as allergies. For example, a patient who experiences vomiting or constipation while receiving morphine is not "allergic" to morphine. Also, patients often mistake a histamine-induced rash as an allergic reaction after the administration of morphine. Previous exposure to similar medications or descriptions of the reaction may help to clarify allergy histories. Getting this information into an electronic database is critical. Patients may not remember their drug allergies. They may describe them in ways that are not useful for computer screening (eg, allergy to "mycins" or "sulfas").

Accurately reporting and communicating allergy information during a patient's hospitalization is as critical as the initial assessment. Physicians can write orders to add or delete allergies from a patient's profile (see core policy CP2.66).*

For example, a nurse may notify the physician about an allergic reaction. The reaction would be treated appropriately and the medication discontinued. If the patient's record is not updated appropriately, pharmacy may dispense a similar drug later, which could cause a similar event. Updating the allergy information could have prevented this second event from occurring.

At the time of discharge, any allergy changes should be explained in detail to the patient. Patients can provide this information to pharmacies in the community and their primary care physicians to help ensure accurate allergy documentation…and the avoidance of future reactions.

LINKS

*https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Policies/CORE/PatientCare/CP2.66_.pdf

Formulary update, *from page 1*

◆ **DELETED (cont.)**

Pilocarpine 0.5% and 6% Ophthalmic Solutions
(Isopto-Carpine® by Alcon)‡

Rosiglitazone
(Avandia® by GlaxoSmithKline)‡§

§Interchanged to pioglitazone

Sulfisoxazole Suspension
(Gantrisin® Pediatric Suspension)‡

◆ **NONFORMULARY AND NOT AVAILABLE**

Doxepin 3 mg and 6 mg
(Silenor® by Somaxon Pharmaceuticals)

Hydromorphone ER
(Exaglo® Neuromed Pharmaceuticals)

Immune Globulin, Subcutaneous
(Hizentra®and Vivaglobulin®)

Velaglucerase Alfa
(Vpriv® by Shire)

Triptorelin Pamoate
(Trelstar® by WatsonPharma)

◆ **INTERCHANGES**

Doxepin 10 mg (Generic) for **Doxepin 3 mg or 6 mg** (Silenor®)

Ferrous Sulfate 325 mg for **Ferrous Sulfate 300 mg**

Pioglitazone (Actos®) for **Rosiglitazone** (Avandia®)

Pravastatin (Generic) for **Pitavastatin** (Livalo®)

The P&T Committee made several changes to the **vitamin D products** listed in the *Formulary*. Vitamin D and its metabolites have significant clinical roles because of their interrelationship with calcium homeostasis and bone metabolism. Vitamin D insufficiency and deficiency, as measured by low concentrations of 25-OH vitamin D, are common, particularly among adolescents and the elderly. Subclinical vitamin D deficiency may contribute to the development of osteoporosis and is associated with an increased risk of fractures and falls in the elderly, decreased immune function, bone pain, and possibly colon cancer and cardiovascular health.

Vitamin D information is prevalent in the medical literature and lay press, which leads to many questions that healthcare professionals have in order to "normalize" vitamin D in deficient patients. Considering the potential health benefits of vitamin D, experts have increased the 200-400 units D_3 daily recommendation to 800-1000 units D_3 per day. This follows recommendations that a serum 25-OH vitamin D level of 30-60 ng/mL should be the goal in order to prevent a rise in serum parathyroid hormone (PTH) and to promote sufficient calcium absorption. Higher doses of 800-1000 units of vitamin D_3 daily are needed to maintain these serum concentrations.

Serum 25-OH vitamin D laboratory tests are expensive, so drawing 25-OH-vitamin D concentrations are usually reserved for the following situations: unexplained signs and symptoms consistent with vitamin D deficiency or toxicity, patients considering supplementation during pregnancy, and patients at known risk of hypercalcemia or hypercalciuria. If a patient is found to be deficient (serum concentrations less than 30 ng/mL), 50,000 units of oral vitamin D_2 weekly for 8 weeks is the preferred treatment, followed by 1000 units of vitamin D_3 daily thereafter for maintenance. If there are concerns about vitamin D concentrations, it is generally accepted not to draw concentrations in patients greater than 50 years of age. These patients should be started on 1000 units vitamin D_3 daily considering the negligible toxicity at this dose and decreased fracture risk.

The *Formulary* listed the following: 200 unit vitamin D_3 tablets (½ tablet), 400 unit vitamin D_3 tablets, **1000 units/mL vitamin D_2 oral liquid** [compounded from the 8000 unit/mL drops and MCT Oil], and a **500,000 unit intramuscular injection vitamin D_2.**

Considering the current vitamin D recommendations, the P&T Committee changed to the following: 200 IU vitamin D_3 tablets (½ tablet), 400 unit vitamin D_3 tablets, **400 unit/mL vitamin D_3 liquid** [added dosage form], **1000 unit vitamin D_3 tablets** [added dosage form], 8000 unit/mL vitamin D_2 drops, and **50,000 unit vitamin D_2 capsules** [added dosage form]. All other dosage forms are nonformulary and not available. Injectable vitamin D_2 is no longer marketed and was designated nonformulary and not available.

Doses [in units] of vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) are not equivalent and should not be interchanged on a unit-per-unit basis. Ergocalciferol is less effective at increasing 25-OH-vitamin D concentrations than cholecalciferol. Based on dosage forms available, it is not possible to establish dose equivalencies to interchange these agents. Prescribers will be contacted and the patient switched to the appropriate dose of available product, as needed.

Leflunomide is a unique disease-modifying antirheumatic drug (DMARD) used for the treatment of rheumatoid arthritis (RA) and juvenile rheumatoid arthritis (JRA). It was evaluated for possible addition in the *Formulary* based on frequent nonformulary use.

Leflunomide is an immunomodulatory agent that is chemically unrelated to other immunosuppressants. It has an active metabolite that inhibits dihydroorotate dehydrogenase, an enzyme involved in pyrimidine synthesis. This prevents T- and B- lymphocytes from cell cycle progression and creates a cytostatic antiproliferative effect. Leflunomide has labeled indications for use in the treatment of active RA to reduce signs and symptoms, inhibit structural damage as evidenced by X-ray erosions and joint space narrowing, and to improve physical function. Leflunomide is included in the recommendations by the American College of Rheumatology (ACR) for treatment of active RA. Off-label use of leflunomide includes the use in JRA and Crohn's disease.

Leflunomide has a long half-life (14–18 days) so a loading dose of 100 mg for 3 days is recommended to reach therapeutic plasma concentrations rapidly. A maintenance dose of 20 mg daily is recommended, but the dose can be decreased to 10 mg daily if the patient is not tolerating the 20 mg dose.

Due to leflunomide's long half-life, a drug elimination procedure has been developed to assist patients in drug clearance. Without the drug elimination procedure, it could take up to 2 years to reach plasma concentrations that are undetectable. The procedure described in leflunomide's labeling recommends using cholestyramine 8 grams 3 times daily for 11 days. The days do not need to be consecutive unless the drug needs to be urgently removed, like in situations of serious adverse effects or confirmed pregnancy.

There have been 3 large, randomized controlled trials evaluating leflunomide versus methotrexate and sulfasalazine. All of the data have shown that leflunomide is as efficacious as methotrexate and sulfasalazine in decreasing tender and swollen joint counts and acute phase reactants (ESR, CRP), improving scores on patient and physician global assessments and patient assessments of pain, and slowing or stopping joint destruction. Leflunomide was superior to methotrexate and sulfasalazine in improvement of physical functioning as evidenced by improvements in the Health Assessment Questionnaire Disability Index and a decrease in length of morning stiffness. This is why leflunomide is the only nonbiologic DMARD with this as an indication.

Leflunomide carries a black box warning to avoid use in women who are pregnant or who may become pregnant. The most common adverse effects of leflunomide are gastrointestinal, abnormal liver function tests (LFTs), rash, alopecia, infections, weight loss, and hypertension. There are a number of other warnings and precautions associated with the drug,

(continued on next page)

Formulary update, *from page 2*

mainly due to immunosuppressive and hepatotoxic effects. Monitoring liver function tests and complete blood counts is important for patients taking leflunomide to avoid serious adverse effects.

Leflunomide has been available as a generic drug for nearly 5 years and is inexpensive.

Benzocaine gel was deleted and designated nonformulary and not available, like benzocaine spray and lozenges, which were designated nonformulary and not available in March. [The spray will be available until June 1st.]

Benzocaine gel is used for the temporary relief of occasional minor irritation and pain associated with canker sores, sore mouth and throat, minor dental procedures, minor injury of the mouth and gums, minor irritation of the mouth and gums caused by dentures or orthodontic appliances.

Based on the uses of benzocaine gel, the alternative topical anesthetics that can be used as an alternative for benzocaine 20% gel are lidocaine 2% gel or lidocaine viscous 2%.

Numerous studies have demonstrated similar efficacy between lidocaine and benzocaine when used for intraoral topical anesthesia. One study also showed the effectiveness of a lidocaine 2% gel in relieving pain following nonsurgical periodontal therapy in patients with periodontitis. Although lidocaine gel and lidocaine viscous are alternatives to benzocaine gel, lidocaine viscous is more palatable.

Cimetidine is the original histamine-H2-receptor antagonist. It was approved as a prescription drug by the FDA in 1977 and became available in a lower dosage in an over-the-counter version in 1995. Its use has steadily decreased since alternative agents, like ranitidine, have fewer adverse effects and drug interactions.

Cimetidine injection is no longer made, presumably because of low demand. Cimetidine tablets are still being marketed, but use has been very low. Therefore, the P&T Committee deleted all forms of cimetidine from the *Formulary*; they were designated nonformulary and not available. Ranitidine (oral and injection) is the alternative listed in the *Formulary*.

Dipivefrin is a prodrug of epinephrine and is an adrenergic agonist that was used for the treatment of open-angle glaucoma. Since it is a prodrug, it supposedly had less systemic effects than epinephrine. It was used off-label to treat ocular hypertension. It is no longer manufactured, presumably because there are better options available. Brimonidine is the most similar drug listed in the *Formulary*.

Ethiodized oil is no longer being made. Ethiodized oil was the only lipophilic non-ionic contrast media. It was an effective contrast agent for lymphography.

The Society for Interventional Radiology is working with the FDA to identify another manufacturer willing to market this product. However, at this time, there is no other alternative. If it re-enters the market, it will be added back in the *Formulary* upon request.

Ganciclovir is an antiviral that was marketed in 1989 for the treatment of cytomegalovirus infections. Ganciclovir capsules have been discontinued by Ranbaxy and are no longer available. There has been a shortage of this antiviral drug, reportedly because of a shortage of raw material; however, Ranbaxy has experienced FDA sanctions for quality issues. A 100-mg/mL compounded ganciclovir liquid, which was made from the capsules, was also deleted from the *Formulary* and designated nonformulary and not available.

Valganciclovir is an alternative listed in the *Formulary*. Usually, a dose of 900 mg of valganciclovir once a day can be substituted for ganciclovir 1000 mg 3 times a day.

Pancrelipase powder is no longer made and will be deleted from the *Formulary* and designated nonformulary and not available once supplies are exhausted.

Pancrelipase products on the market have been unapproved drugs. The FDA issued a mandate in 2004 requiring manufacturers of pancreatic enzyme replacement products to seek approval through the NDA process. There have been concerns about lack of standardization and equivalency. In Florida, these products are listed in the *Negative Formulary*.

Although pancrelipase powder was labeled for use in patients with pancreatic insufficiency, it was mainly used to unclog occluded feeding tubes when mixed with sodium bicarbonate. Crushed pancrelipase tablets and other devices for this purpose are being evaluated as alternatives. It is estimated that we have sufficient pancrelipase powder to last until around July 2010.

Pilocarpine is a topical muscarinic agent used in the eye for miosis and the treatment of glaucoma. The 0.5% and 6% strengths have been discontinued. The 1%, 2%, and 4% drops, which are more commonly used, remain in the *Formulary*.

Rosiglitazone is a thiazolidinedione or "glitazone" oral antidiabetic agent. **Pioglitazone** [Actos®] is the other commonly used agent in this class. Both of these agents have been listed in the *Formulary*. Pioglitazone was added in the *Formulary* in June 2007 after questions about the cardiovascular safety of rosiglitazone were first raised. Previously, patients on pioglitazone were being interchanged to rosiglitazone.

The FDA continues to evaluate the cardiovascular safety of rosiglitazone and it is generally accepted that pioglitazone has a better safety profile. Both agents work equally well at lowering blood glucose (at equipotent doses), although neither is very potent.

About 5 patients are admitted on pioglitazone for each patient admitted receiving rosiglitazone, although neither agent is used commonly. The P&T Committee approve the interchange of rosiglitazone to pioglitazone.

INTERCHANGE OF ROSIGLITAZONE TO PIOGLITAZONE

Pioglitazone 15 mg for Rosiglitazone 2 mg

Pioglitazone 30 mg for Rosiglitazone 4 mg

Pioglitazone 45 mg for Rosiglitazone 8 mg

Sulfisoxazole pediatric oral suspension has been discontinued and there is no alternative source. Sulfisoxazole is a sulfonamide antibiotic. It was designated nonformulary and not available.

Silenor® is a new brand name for an old drug, **doxepin**, which is being marketed for the labeled indication of the treatment of insomnia in patients who have difficulty remaining asleep. Doxepin was originally approved by the FDA in 1969 as a tricyclic antidepressant with 150 mg per day a common dosage. Because of its sedative properties, it was also labeled for the treatment of anxiety. It is also a potent H1-antihistamine and has been used off-label for its systemic antihistamine effects and topically for a labeled indication of eczema.

Silenor® will be available in 3- and 6-mg tablets. A 10-mg oral solid dosage form has been the lowest available oral solid dosage form of generic doxepin. There is a generic 10 mg/mL oral solution; however, this product is not currently listed in the *Formulary*.

The P&T Committee designated Silenor® nonformulary and not available and designated automatic interchange of 3- or 6-mg doses of doxepin to doxepin 10 mg.

Exaglo® is an **extended-release** tablet dosage form of **hydromorphone**. It has a labeled indication for the management of moderate-to-severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period. It is not intended for use as an "as needed" analgesic.

Exaglo® is a nonformulary controlled substance (CII); thus, patients cannot use their own supply from home. The P&T Committee designated Exaglo® nonformulary and not available. Alternative extended-release opioids in the *Formulary* include oxycodone extended-release and morphine extended-release.

(continued on next page)

Drugs & Therapy
B · U · L · L · E · T · I · N

Volume 24, No. 5 May 2010
This publication is produced by the Drug Information and Pharmacy Resource Center under the direction of the Department of Pharmacy Services and the Pharmacy and Therapeutics Committee.

EDITOR, DRUGS & THERAPY BULLETIN
Randy C. Hatton, PharmD

DIRECTOR, PHARMACY SERVICES
Alan Knudsen, MS, RPh

CHAIRMAN, PHARMACY & THERAPEUTICS COMMITTEE
Ricardo Gonzalez-Rothi, MD

EDITING, DESIGN, & PRODUCTION
Shands HealthCare's Publication Svcs.

FOR MORE INFORMATION, VISIT US ONLINE
http://shands.org/professionals/druginfo/bulletin.asp

SHANDS
Shands at the University of Florida
DRUG INFORMATION SERVICE
PO Box 100316
Gainesville, FL 32610-0316

NON-PROFIT ORG.
U.S. POSTAGE
PAID
GAINESVILLE, FL
PERMIT NO. 94

Formulary update, from page 2

Subcutaneous immune globulins (SCIGs) are alternatives to intravenous immune globulins (IVIGs) in patients with primary immunodeficiencies. SCIGs are given weekly, instead of monthly for IVIGs. The main advantage of SCIGs is that the patients may be treated at home, as opposed to going to an infusion center for their monthly IV dose.

Hizentra® is a new SCIG. **Vivaglobulin**® was the first marketed SCIG. The P&T Committee determined that there is no indication for SCIGs in the inpatient settings. If patients experience adverse effects from IVIG, the infusion rate should be slowed during their inpatient admission to minimize infusion-related effects (eg, headache).

Velaglucerase alfa is an intravenous replacement therapy used for the long-term treatment of patients with Gaucher's disease. Gaucher's disease occurs in about 1 in 50,000 to 1 in 100,000 people. Velaglucerase is an alternative to imiglucerase [Cerezyme®] or alglucerase [Ceredase®], which have never been listed in the *Formulary*. Alglucerase is no longer marketed, and imiglucerase has been in short supply because of production problems (ie, a virus contamination of the cell cultures producing the drug). Neither Cerezyme® nor Ceredase® has ever been listed in the *Formulary*.

Velaglucerase alfa replaces the endogenous enzyme beta-glucocerebrosidase. Without this enzyme, harmful amounts of certain lipids can build up in the liver, spleen, bones, bone marrow, and nervous system causing organ dysfunction. Velaglucerase is available only via a restricted-distribution program (ONEPATH).

Consistent with other drugs in this category, velaglucerase alfa was designated nonformulary and not available. Patients may use their own supply when they are hospitalized.

Trelstar® is **triptorelin**, an every 4 to 12 week intramuscular gonadotropin releasing hormone (GnRH) antagonist. It has a labeled indication for the palliative treatment of advanced prostate cancer. Like many other intermittent drugs for this indication, it was designated nonformulary and not available. Inpatient reimbursements do not cover the increased expense associated with the use of this agent.

Ferrous sulfate is a commonly used form of oral iron supplementation for the treatment or prevention of iron deficiency anemia. Ferrous sulfate delivers 20% elemental iron. Common oral dosages include both 300 mg and 325 mg (ie, 5 grains). The 300-mg tablets are no longer available, and we are able to obtain only 325-mg tablets.

Rather than call the prescriber each time ferrous sulfate 300 mg is ordered, the P&T Committee approved an automatic interchange to 325 mg. The typical dose of elemental iron for adults and adolescents with iron deficiency anemia is 50 to 100 mg given 3 times a day orally. A 325-mg dose of ferrous sulfate delivers 65 mg of oral iron; thus, the typical dosage for ferrous sulfate is 325 mg orally 3 times a day.

Pitavastatin is an HMG-CoA reductase inhibitor or statin that was approved by the FDA in August 2009. It is expected to be marketed in 2010. When it was first approved by FDA, the P&T Committee proactively deemed it nonformulary and not available (although patients could use their own supply) with an automatic interchange. This interchange was based on noninferiority trials that showed similar efficacy in adult patients (ie, simvastatin 10 mg equals pitavastatin 1 mg).

A review of the pharmacology of pitavastatin revealed that one of its features is that it does not interact with CYP 3A4. Therefore, the interchange was modified and pitavastatin will now be interchanged to pravastatin instead of simvastatin (since pravastatin also does not have CYP 3A4 drug interactions). Now, pravastatin 20 mg will be substituted for each 1-mg dose of pitavastatin.