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Shands at the University of Florida

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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met October 16, 2007. 2 drugs or dosage forms were added in the *Formulary*, and 2 dosage forms were deleted. 3 drugs or dosage forms were designated nonformulary and not available. The use of 1 drug in the *Formulary* was restricted.

◆ ADDED

Cinacalcet
(Sensipar® by Amgen)

Sodium Chloride Tablets
(generic)

◆ DELETED

Lansoprazole Delayed-Release Suspension
(Prevacid® Packets by TAP Pharmaceuticals)*

Tetracycline Syrup
(generic)*

**Nonformulary and not available*

◆ NONFORMULARY AND NOT AVAILABLE

Lubiprostone
(Amitiza® by Takeda Pharmaceuticals)

◆ CRITERIA-FOR-USE CHANGES

Corticotropin Repository Injection (Acthar® Gel by Questor Pharmaceuticals)†

†Restricted to approval by Pediatric Neurology for infantile spasms

Cinacalcet was evaluated for possible addition in the *Formulary* because of high-volume nonformulary use. Cinacalcet is an oral calcimimetic agent that was approved by the FDA in March 2004. It is the only agent in its therapeutic class. Cinacalcet has labeled indications for use in the treatment of secondary hyperparathyroidism in patients

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POLICIES AND PROCEDURES

Standardized dosing times

Standard medication administration times have existed for many years. These times are in place to improve efficiency and communication. The administration times have been modified recently based on feedback received from the Departments of Nursing and Pharmacy. When dosing times are not specified by the prescriber, the default times in the table (see below) will be used.

There will be a series of educational sessions scheduled with the medical and nursing staffs to go over the more subtle implications of the new policy. These sessions will emphasize to prescribers that "3 times a day" is not the same as "every 8 hours." For oral drugs, every-8-hour dosing requires that patients be awakened to receive their dose. Waking the patient may or may not be necessary, depending on the medication.

STANDARDIZED DOSING TIMES

Interval	Standard Times
Daily	0900
2 times a day (BID)	0900, 2100
3 times a day (TID)	0900, 1400, 2100
	0800, 1200, 1700 (52 Psych)
4 times a day (QID)	0900, 1300, 1700, 2100
5 times a day	0500, 0900, 1300, 1700, 2100
Every 3 hours	0000, 0300, 0600, 0900, 1200, 1500, 1800, 2100
Every 4 hours	0100, 0500, 0900, 1300, 1700, 2100
Every 6 hours	0600, 1200, 1800, 2400
Every 8 hours	0800, 1600, 2400
Every 12 hours	0900, 2100
Every 24 hours	Time will default to hour profiled (ie, 1st order processed)
Bedtime	2100
With meals	0800, 1200, 1700
With meals and at bedtime	0800, 1200, 1700, 2100
Injectable antibiotics	Times determined by the time the 1st dose is processed

There are several medications that have unique specified dosing times: to allow laboratory values to be evaluated before the dose is given (ie, warfarin , epoetin, darbepoetin, and filgrastim at 1800); to avoid meals (ie, oral fluoroquinolones at 0600 and 1600 [meals are generally given at 0800, 1200, and 1700]); convention (ie, cyclosporine at 0800 and 2000); for patient convenience (ie, furosemide at 0900 and 1800); and, to improve efficacy (ie, statins at bedtime).

Because injectable antibiotics should be started as soon as possible and prolonged intervals could affect efficacy, the dosage time for injectable antibiotics will be determined by the time of the first dose. For example, a twice daily injectable antibiotic order is received at 1400. The first dose will be scheduled for 1500. Subsequent doses will be given at 0300 and 1500.

For more information on standardized dosing times or to schedule an inservice on this topic, contact Dr. Erin Jones in the Department of Pharmacy Services at 265-0404.

INSIDE THIS ISSUE

Formulary update, *from page 1*
with chronic kidney disease on dialysis and for the treatment of hypercalcemia in patients with parathyroid carcinoma.

Chronic kidney disease is associated with hyperphosphatemia, hypocalcemia, and increased stimulation of the parathyroid gland. These alterations lead to secondary hyperparathyroidism, a progressive condition that eventually results in bone disease and calcification of vascular and soft tissues.

Cinacalcet acts on the calcium-sensing receptor on the surface of the chief cell in the parathyroid gland. The calcium-sensing receptor is the principal regulator of parathyroid hormone (PTH) secretion. By mimicking calcium, cinacalcet increases the sensitivity of the calcium-sensing receptor to extracellular calcium and lowers PTH levels. Decreased serum calcium is associated with reduction in PTH. After 1 week of therapy, reduction in serum calcium is seen and maintained.

Managing patients, according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines on bone metabolism and disease in chronic kidney disease, can be challenging. Traditional therapies for stage 5 chronic kidney disease include phosphate-binders and vitamin D sterols and can be associated with hypercalcemia.

Evidence from randomized, placebo-controlled trials in dialysis patients shows that cinacalcet is effective in reducing intact PTH while also reducing serum calcium, phosphorus, and calcium-phosphorus product. At the start of these studies, patients had elevated PTH in spite of treatment with phosphate binders and/or vitamin D sterols. At this time, a large prospective, randomized, placebo-controlled trial is being conducted to determine if cinacalcet reduces the risk of mortality or cardiovascular events in hemodialysis patients.

The most common adverse events associated with cinacalcet use are nausea and vomiting. Cinacalcet may be associated with increased risk of seizures, hypocalcemia, and adynamic bone disease. Drug interactions involving the cytochrome P450 enzyme system are possible with concomitant cinacalcet therapy. Increased monitoring of serum calcium and PTH may be necessary to manage the risks of severe adverse events.

Compared with other oral medications, cinacalcet is quite expensive. Based on typical dosages, it will cost approximately $1000 per month.

Sodium chloride tablets were deleted from the *Formulary* during a time of shortage. The shortage has been resolved, and there is now a need to re-add this dosage form back in the *Formulary.*

The new enteral feeding system used by Dietary Services does not allow the addition of specific electrolytes. Extra sodium chloride must be administered separately. This is usually done using sodium chloride 4 mEq/mL injection in an oral syringe. However, adult and older pediatric patients who can take oral solids can be supplemented with 1-gram sodium chloride tablets (ie, delivering 17.2 mEq of sodium per tablet).

Prevacid® for Delayed-Release Oral Suspension Packets will no longer be marketed by TAP Pharmaceuticals. This product is not used much; other dosage forms are more popular. The packets were deleted from the *Formulary* and designated nonformulary and not available.

Lansoprazole suspension compounded using sodium bicarbonate is a better alternative for administering lansoprazole down a feeding tube. Prevacid® Oral Suspension Packets produced a thick suspension because it contained xanthan gum to increase viscosity. This thick suspension often clogged feeding tubes, especially small-bore feeding tubes.

Prevacid® SoluTabs® have a pleasant taste and can be used to administer lansoprazole orally in small children who cannot swallow capsules. The SoluTabs® can also be dissolved in a small amount of water and administered down a feeding tube. The granules in the SoluTabs® do not clump or stick to the feeding tube.

Tetracycline syrup has been discontinued by its manufacturer. There is no alternative source. After consulting with the Infectious Diseases Subcommittee, there appears to be no need to recommend an alternative agent. Tetracycline syrup was designated nonformulary and not available.

Lubiprostone was evaluated for possible addition in the *Formulary* based on requests for use and potential for inappropriate off-label use.

Lubiprostone is a member of a new class of bicyclic fatty acids prostaglandin E_1 derivatives known as prostones. It increases intestinal fluid secretion via a novel mechanism of action by specifically activating type 2 chloride channels. The secretions subsequently soften the stool, increase intestinal motility, promote spontaneous bowel movements, and relieve signs and symptoms of constipation.

Lubiprostone is administered orally and has low systemic availability. Plasma concentrations are below the level of detection; there are no known drug interactions. A clinically meaningful effect usually occurs within 1 week of administration, and tolerance to use has not been observed during clinical trials. Additionally, a sustained response has been shown 3 weeks after stopping therapy.

Lubiprostone, which was approved by the FDA in January 2006, currently only has an FDA-labeled indication for the treatment of chronic idiopathic constipation. The labeled dose is 1 capsule (24 mcg) twice daily with meals. The drug has not been specifically studied in patients with hepatic or renal impairment, but the need for dosage adjustments is unlikely as it has minimal systemic availability. Safety and efficacy have not been established in children or adolescents. A lower strength of lubiprostone (ie, 8 mcg) to treat irritable bowel syndrome with constipation is currently under review by the FDA.

There are no head-to-head studies comparing lubiprostone to other agents used to treat chronic constipation (ie, bulk-forming fiber products or stool softeners). The approval of lubiprostone was primarily based on 2 randomized, double-blind, placebo-controlled, phase 3 trials that showed moderate improvements in weekly bowel movements (ie, an absolute increase of approximately 2 bowel movements per week [approximately 3 vs 5]). Also, only approximately 60% of patients had a spontaneous bowel movement in the first 24 hours of treatment.

The most commonly reported adverse effect during clinical trials was nausea. The incidence of nausea is dose-related; 8% of patients discontinued treatment during trials due to nausea. Other common side effects during trials included diarrhea, headache, and abdominal pain or distension.

Chronic constipation is primarily treated on an outpatient basis. There are various low-cost formulary options available for acute treatment of constipation (eg, senna), as well as fiber products and stool softeners for possible prevention. Patients admitted who are already taking lubiprostone may take their own supply or be treated with other formulary agents for constipation during hospitalization. Additionally, discontinuation of lubiprostone does not result in a rebound effect and, in fact, shows a sustained response 3 weeks after stopping the drug. Therefore, lubiprostone was designated nonformulary and not available.

Acthar® Gel remains listed in the *Formulary;* however, it is now restricted to prior approval by Pediatric Neurology for use in the treatment of infantile spasms. Product will not be stocked for use in the hospital and will be obtained only for use in patients who have been approved for use in the product's restricted-distribution program.

The changes in the formulary status of Acthar® Gel are the result of Questor Pharmaceuticals' recent announcement that it increased the cost of a 5-mL multi-dose vial (80 units/mL) from its previous price of about $1,500

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Formulary update, *from page 2*
per vial to $23,000 per vial! This is more than a 15-fold increase. The manufacturer states this price is in line with other drugs that are used to treat rare disorders.

Shands at UF has been a relatively heavy user of Acthar® Gel. Without the current restrictions, there could have been an increase in pharmaceutical expenditures of $1.4 million.

A review of the last year's Acthar® Gel use showed that most was being used for the treatment of acute gout. There are multiple alternative agents that can be used to treat an acute exacerbation of gout. Nonsteroidal anti-inflammatory agents (NSAIDs) and colchicine are commonly used. However, patients who cannot tolerate an NSAID or colchicine can be treated with corticosteroids. Intra-articular steroids are an option when 1 or fewer joints are involved. There are several other oral and parenteral alternatives to Acthar® Gel.

Oral prednisone (20-60 mg per day tapered over 10 days) is an option for patients who can take oral medications. Intramuscular or intravenous methylprednisolone (100 mg per day with taper) is another inexpensive alternative. There are also data supporting the use of a 60-mg dose of intramuscular triamcinolone acetonide for the treatment of gout, but this is nearly 17-times more expensive than methylprednisolone.

Cosyntropin (Cortrosyn®), a synthetic form of adrenocorticotropic hormone (ACTH) that contains the biologically active amino acid portion of ACTH, can be used as an alternative to Acthar® Gel for the treatment of gout. Cosyntropin has less antigenicity than natural ACTH.

Studies showing benefit from ACTH in gout did not use synthetic ACTH. However, cosyntropin does stimulate the adrenal cortex maximally and to the same extent as an equivalent dose of natural ACTH. Additionally, the common extra-adrenal effects including increased melanotropic activity, increased growth hormone secretion, and adipokinetic effects are also similar.

According to Cortrosyn® labeling, 25 units of corticotropin is pharmacologically equivalent to 0.25 mg cosyntropin based on the level of stimulation on the adrenal cortex. Based on this conversion, 0.4 to 0.8 mg of cosyntropin would be an equivalent dose for treating gout (ie, equal to a 40 to 80 unit dose of Acthar® Gel). This treatment is as much as 300 times more expensive than methylprednisolone. Acthar® Gel is about 15 times more expensive than cosyntropin. A table with drug, dosage, and cost comparisons of drugs used for the treatment of acute gout can be found on the intranet at http://intranet.shands.org/pharm/Acute_Gout_Rx.pdf.

Acthar® Gel has also been used to treat multiple sclerosis exacerbations. There are other alternatives (eg, methylprednisolone) that are preferable in this condition.

NEWS

Medical foods: Drug, dietary supplement, food, or other?

What is a medical food? Is it a drug? Is it a dietary supplement? Is it a food? Or maybe it's something else entirely? If you answered "something else entirely," you are correct.

The term "medical food" is officially defined by the FDA in a section of the Orphan Drug Act Amendments of 1988. The term "medical food" does not simply apply to all foods fed to sick patients. A medical food is "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."A couple key points are: physician supervision, taken orally, and taken for a specific nutritional need for a certain condition. A medical food is NOT required to be prescription only; over-the-counter products can be used under medical supervision.

So how are medical foods regulated? Since they fall into a unique class they are regulated differently than both drugs and dietary supplements.

Medical foods do NOT have to undergo pre-marketing review or be approved by the FDA; individual medical food products do not have to be registered with the FDA. Additionally, medical foods are exempted from the labeling requirements for health claims and nutrient content claims under the Nutrition Labeling and Education Act of 1990. As a result, medical foods are not limited to the "structure/function" claims for dietary supplements. Manufacturers can make disease-specific statements for these products.

Medical foods are foods, however, and are at least required to have a certain amount of labeling. This must include: a statement of identity; an accurate statement of the net quantity of contents; name and place of business of the manufacturer, packer, or distributor; and a complete list of ingredients. Also the Food Allergen Labeling and Consumer Protection Act (FALCPA) require that medical foods include on the label the food source name of any major allergens (ie, peanuts, eggs, shellfish). Furthermore, medical foods must comply with all applicable requirements for the manufacture of foods in general, such as the Current Good Manufacturing Practices regulations.

So what are the implications of the lax regulation of medical foods? Due to lack of regulatory control, the FDA historically has paid little attention to medical foods. This created an environment wherein manufacturers — taking advantage of an opportunity not to have to get FDA approval — started to market a variety of food products as medical foods, regardless if they qualify as such.

Based on possible safety concerns, the FDA has recently developed a Compliance Program specifically for medical foods. This program enables FDA inspectors to do the following: (1) obtain information regarding the manufacturing/control processes and quality assurance programs employed by domestic manufacturers of medical foods through establishment inspections, (2) collect domestic and import surveillance samples of medical foods for nutrient and microbiological analyses, and (3) take action when significant violations of the Federal Food, Drug and Cosmetic Act (or related regulations) are found.

What medical foods are available? The prototypical example of a medical food is the phenylalanine-free nutritional supplement (PhenylAid®) for patients with phenylketonuria (PKU). Other examples of products that claim to be medical foods include: L-methylfolate (Deplin®) for depression; flavocoxid (Limbrel®) for osteoarthritis; lactic acid bacteria (VSL#3®) for ulcerative colitis, IBS, or ileal pouch; Complex MSUD® Drink Mix for branched-chain alpha-keto acid dehydrogenase deficiency (Maple Syrup Urine Disease); UltraClear® for chronic fatigue syndrome; Estrium® for symptoms related to the "female hormone cycle"; UltraGycemX® for conditions associated with type 2 diabetes; and TramaCal® Liquid for metabolically stressed patients (eg, burn patients). Many of these products have a Web page if you are interested in additional information; however, some of the claims made for these products are not backed by the standards of evidence that we would expect for drugs.

By Russell McKelvey, PharmD

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