

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met June 19, 2012. 2 products were added in the *Formulary* and 3 were deleted from the *Formulary*. 6 products were designated nonformulary and not available and 1 interchange was approved. 1 P&T approved order was approved to help improve the administration of post-dialysis doses.

◆ ADDED

Ezogabine (Potiga®)

Sodium Hypochlorite 0.0125%
(Di-Dak-Sol®)*

*Also known as *Diluted Dakin's Solution*

◆ DELETED

Sodium Hypochlorite 0.5%
(Dakin's Full-Strength)†

Sodium Hypochlorite 0.25%
(Dakin's Half-Strength)†

Sodium Hypochlorite 0.125%
(Dakin's Quarter-Strength)†

†Nonformulary and not available effective 8/21

◆ NONFORMULARY AND NOT AVAILABLE

Avanafil (Stendra®)

**Azelastine + Fluticasone
Nasal Spray** (Dymista®)

Taliglucerase Alfa (Elelyso®)‡
‡Patients must use their own supply

◆ INTERCHANGES

**Azelastine + Fluticasone
Nasal Spray** (Dymista®)§

§Interchanged to the individual ingredients

◆ ADDITIONAL ISSUES

Post-Hemodialysis Dose Reminder[¶]
¶P&T Approved Order mode to a MAR reminder for post-dialysis doses

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NEWS

Medicaid restricts oxycodone prescribing for children

Since June 7, 2012 Florida Medicaid has required prior authorization for all prescriptions for single-ingredient opioids containing oxycodone (ie, liquid, immediate-release, and extended-release products) for all patients less than 18 years of age. The State instituted this restriction because the parents of some patients were using these prescriptions to obtain oxycodone for illicit use. "Oxy" abuse has reached epidemic proportions.

The Florida Medicaid prior-authorization process can take up to 48 hours, which can be problematic if you are not aware of this restriction and try to prescribe oxycodone for acute pain. When a prescription is written for a single-ingredient oxycodone product after surgery, it will be denied at the pharmacy trying to fill it if there is no prior authorization.

Since oxycodone is a schedule II controlled substance, it may be difficult for the patient to receive an alternative product. The patient would have to return to the hospital to get another written prescription for a different schedule II pain medication. This could lead to the patient not receiving the appropriate pain relief.

There is no restriction on other schedule II opioids. Therefore, prescribers should consider oral codeine, morphine, or hydromorphone for acute pain. These prescriptions do not require prior authorization.

Florida Medicaid also does not restrict oxycodone containing combination products (ie, products containing acetaminophen). Therefore, prescriptions for drugs like Percocet® or Tylox® are not restricted.

The rationale for this exception is that acetaminophen-containing products have less abuse potential. When patients ingest too much acetaminophen per day, acutely or chronically,

it can result in serious liver toxicity. If these combination products are prescribed, please remind parents that they should not give additional acetaminophen for pain or fever, which could push the total daily dose beyond what can be safely administered in a day and could cause hepatotoxicity. The maximum daily dosage of acetaminophen for a child is 75 mg per kilogram (ie, 15 mg per kilogram up to 5 doses that are separated by 4 to 6 hours) or a maximum of 4 grams per day, which is the maximum daily dosage for adults.

Since oxycodone-acetaminophen prescriptions are still schedule II controlled substances, they cannot be phoned in as a substitute for a prescription denied by Medicaid because of a lack of prior authorization. Hydrocodone-acetaminophen combinations (ie, Lortab® or Vicodin®) are schedule III controlled substances and could be phoned into a pharmacy as an alternative for acute pain.

For patients less than 18 with chronic pain (eg, cancer patients), who cannot be treated with a different opioid, obtain authorization from Florida Medicaid ahead of time to prevent any delay in filling these patients' chronic prescriptions. You can do this by going to the Florida Medicaid Pharmacy Prior Authorization Form website and selecting the miscellaneous form (http://ahca.myflorida.com/Medicaid/Prescribed_Drug/pharm_thera/paforms/miscellaneous.pdf). Note on the form that you would like an age exemption for the oxycodone restriction and fax the request to (877) 614-1078.

INSIDE THIS ISSUE

◆ TNF-alpha restrictions?

Ezogabine is a potassium-channel opener, which is a new class of drugs. It has a labeled indication for use in patients as adjunctive treatment for partial-onset seizures in patients over the age of 18. It has not been approved for use as monotherapy or for patients under the age of 18.

Ezogabine has its greatest effect at the neuronal KCNQ potassium channels. Seizure activity is reduced by activation of the potassium channels causing membrane repolarization and by augmentation on the GABA-evoked currents. Because of its ability to cross the blood-brain barrier, most common adverse events are central nervous system-related. Most adverse effects are associated with dose escalation and are more commonly seen at higher dosages (900 mg-1200 mg/day).

Dose titration to effectiveness is required and the manufacturer has specific recommendations for dose titration and discontinuation of therapy for both general and special populations, underscoring the importance of continuity of treatment. The maximum effective dose for the general population is 400 mg by mouth 3 times daily (1200 mg/day).

Ezogabine elimination occurs primarily by the renal route, with some metabolism via glucuronidation and acetylation to N-glucuronides and NAMR, an active metabolite. Dosage reductions are required in renal and hepatic impairment.

There is no evidence that it is metabolized by the cytochrome P450 system so interactions with drugs that are metabolized by this system are not anticipated, although phenytoin and carbamazepine may decrease ezogabine levels.

Ezogabine is a pregnancy category C drug, does not cause infertility/reproductive performance issues, and has unknown effects on lactation. Women who become pregnant on this drug should enroll in the North American Antiepileptic Drug (NAAED) Pregnancy registry. Safety and effectiveness in pediatric patients has not yet been established.

Because ezogabine affects potassium channels, there is some concern about effects on the heart, especially the QT interval. Ezogabine did prolong QT interval about 8 msec in healthy volunteers, and it should be used with caution with other drugs that also prolong the QT-interval.

Other potential adverse effects include urinary retention, confusion, psychotic symptoms, hallucinations, dizziness, somnolence, and suicidal ideation. Abruptly stopping ezogabine could increase seizure activity. Tapering over 3 weeks is recommended if ezogabine is discontinued.

Placebo-controlled clinical trials support the benefit of ezogabine versus placebo in adult patients with partial-onset seizures refractory to treatment with 1-3 other antiepileptics at stable doses. No comparative effectiveness research is available comparing ezogabine to other antiepileptics.

Ezogabine is expensive, costing as much as \$20 per day. Because the anticipated use is low, it should not add significantly to pharmaceutical expenditures. Many other agents can be used to treat and control seizure activity and ezogabine use should be limited to patients that are refractory to other therapies.

If a patient is admitted and currently maintained on ezogabine, it should be continued during the admission because of tapering requirements at initiation and discontinuation. Furthermore, ezogabine is a schedule V controlled substance precluding patients from taking their own medication. Unless use is higher than expected (ie, off-label use), restrictions should not be necessary. Therefore, ezogabine was added in the *Formulary*.

Full-, Half-, and Quarter-Strength Dakin's Solutions were deleted from the *Formulary* and designated nonformulary and not available. **Diluted Dakin's Solution** was added as an alternative to these topical disinfectants. Because of logistical issues, these decisions will be implemented August 21, 2012.

Dakin's solution is a solution of **sodium hypochlorite**. It was created during World War I to treat infected wounds. It is not an FDA-approved drug. Traditionally, Dakin's Solution has been used as a topical wound irrigation product due to its antiseptic activity. It is a bactericidal product that works via direct contact with hypochlorous acid, a strong oxidizing agent. Its use as a topical antiseptic stems from its ability to kill bacteria at the wound site while avoiding systemic antimicrobial toxicities.

Dakin's has been shown to be an effective antimicrobial agent but its effects on human tissues at higher concentrations are concerning. A study by Heggers and colleagues investigated safety concerns with Dakin's Solution. Concentrations of 0.25%

(Half-Strength Dakin's Solution), 0.025%, and 0.0125% were studied for toxicities in mouse fibroblasts compared to those treated with distilled water. The mouse fibroblasts exposed to the 0.0125% concentration were comparable to those treated with distilled water after 7 days of exposure. Those exposed to the 0.25% solution showed cell death and disruption of the cytoarchitecture after 10 minutes of exposure. Fibroblasts exposed to the 0.025% solution maintained their architecture and viability. These results support the use of lower concentrations of hypochlorite solution. Diluted Dakin's Solution (0.0125%), which is available as a commercially stable product, may yield the optimal balance between antimicrobial killing and impairment of wound healing.

The labeling of Dakin's Solution has safety concerns. The strengths are listed as full-strength, half-strength, and quarter-strength but the actual concentrations are as follows: Full-Strength Dakin's is a 0.5% solution, Half-Strength is a 0.25% solution, and Quarter-Strength is a 0.125% solution. This nomenclature may contribute to potential medication errors.

A commercially available product is stable for approximately 12 months, while a compounded product would be stable for 30 days. Also, there is no commercially available hypochlorite solution at a concentration of 0.025%, which is one of the most commonly studied strengths that showed an optimal benefit to risk ratio. Therefore, only Diluted Dakin's Solution (0.0125%) will be listed in the *Formulary* for topical antiseptic use.

Di-Da-Sol® will replace Dakin's Solutions in the *Formulary* on August 21, 2012. Orders for oxychlorosene will be changed to Di-Dak-Sol® after this date.

Avanafil is another phosphodiesterase type 5 (PDE5) inhibitor approved with a labeled indication for the treatment of erectile dysfunction. It is approved for once-daily dosing and may offer benefit over other PDE5s via a faster onset of action. It has not yet been studied in pulmonary hypertension. Two formulary agents (sildenafil and tadalafil) are available in the *Formulary* to treat pulmonary hypertension. Therefore, avanafil was designated nonformulary and not available.

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Formulary update, from page 2

Dymista® is a nasal spray containing an H1-receptor antagonist (azelastine) and a corticosteroid (fluticasone propionate) indicated for the relief of symptoms of seasonal allergic rhinitis. It contains azelastine and fluticasone propionate at doses of 137 mcg and 50 mcg, respectively, per spray.

Azelastine 137 mcg/spray nasal spray was added to the *Formulary* in March 2012. Additionally, fluticasone was designated the preferred nasal spray in August 2010, with an interchange approved for all other nasal sprays. Therefore, Dymista® will be interchanged to its component medications, at an equivalency of 1 spray of Dymista® for 1 spray each of azelastine and fluticasone nasal sprays.

Taliglucerase alfa was approved by FDA with a labeled indication for enzyme replacement treatment in patients with a confirmed diagnosis of Type I Gaucher's disease. Gaucher's disease is a lysosomal storage disease that is caused by a hereditary deficiency of glycosylceramidase. The accumulation of glucocerebrosides in the spleen, liver, kidneys, lungs, brain and bone marrow results in multiple symptoms. Symptoms include bruising, fatigue, anemia, low platelets, and enlargement of the liver and

spleen. Patients with multiple organ dysfunction may be more susceptible to infection.

Taliglucerase alfa is a beta-glucocerebrosidase that breaks down glucocerebrosides. It is produced by recombinant DNA technology using plant cell culture, which eliminates the threat of viruses and other pathogens that can contaminate mammalian stocks.

Taliglucerase alfa is administered every other week. Imiglucerase and alglucerase are administered 3 times weekly. The cost of these drugs can be extremely high, up to \$300,000 per year.

Similar drugs, including imiglucerase, have been designated nonformulary and not available requiring patients to use their own supply. Therefore, taliglucerase alfa was designating nonformulary and not available requiring patients to use their own supply.

A post-dialysis dose reminder was approved by the P&T Committee. Doses of post-hemodialysis medications may be missed because there is no eMAR notification to remind nurses that a dose is due when the patient returns from a hemodialysis session. Variability in dialysis schedules makes it impossible to set a standard due time for the post-hemodialysis dose on the eMAR.

Pharmacy and nursing have agreed on a new process to help reduce the number of missed post-hemodialysis doses. A

new reminder order has been created in Epic that will appear on the patient's eMAR if they have a medication that must be administered after dialysis. This order will serve as a reminder for the nurse to review whether the patient received hemodialysis that day and if so, administer the post-hemodialysis medication (if not already administered). The eMAR reminder will appear with a due time of 1600.

Order panels will be created in Epic for commonly prescribed post-hemodialysis medications (vancomycin, aminoglycosides, and piperacillin-tazobactam). This panel is comprised of 2 orders, the drug order, and the eMAR reminder order. These orders are linked so that when the drug is discontinued, the physician will be prompted to discontinue the reminder order as well.

If prescribers do not select the hemodialysis order panel, the eMAR reminder order is not automatically placed. A pharmacist may now enter an eMAR reminder order using the "P&T Approved Change" order mode when a post-hemodialysis medication is ordered without a reminder. This order mode does not require a physician co-signature. Pharmacists will link the eMAR reminder with the original post-HD medication order.

PROPOSAL

Should the inpatient use of TNF-alpha drugs be restricted?

Adalimumab, certolizumab, etanercept, and golimumab are subcutaneously administered monoclonal antibodies that neutralize tumor necrosis factor-alpha (TNF-alpha). TNF-alpha is a pro-inflammatory cytokine that plays an important role in several autoimmune inflammatory conditions. TNF-alpha drugs are used in the treatment of rheumatoid arthritis (RA), Crohn's disease, and various off-label indications. They are currently not listed in the *Formulary* and because they are injectable drugs, patients cannot use their own supply.

Inpatient use of these products presents several concerns including whether patients should be allowed to use their own subcutaneous (SQ) injectable medications, the financial impact of fixed reimbursements that do not consider the high cost of these drugs, and the risk of infections while using these immunosuppressive drugs.

Use of these agents might be most logical for patients with long hospital stays where missing doses could be detrimental to a patient's long-term prognosis. However, there are studies that suggest that it is not critical to administer a dose simply because it is due and that an interruption in therapy would not be significant for most patients.

There are limited data available to determine relative efficacy and safety for adalimumab, certolizumab, etanercept, and golimumab. There are meta-analyses of placebo-controlled trials and systematic reviews. There are no head-to-head comparisons of these products. All agents are more effective compared to placebo and appear efficacious for their labeled indications. However, 2 meta-analyses suggest that golimumab is less efficacious than adalimumab, certolizumab, and etanercept in the treatment of RA.

Because therapy is often interrupted by cost barriers, several studies have evaluated the effect of treatment interruptions and resumptions. These studies suggest a sustained duration of action following interruption that is unlikely to be clinically relevant for several weeks. Additionally, the majority of patients continue to respond with treatment re-initiation. No study has evaluated the onset of action, though trials do not measure response sooner than 4 weeks.

For some hospitalized patients, risks will outweigh benefits associated with use. These agents pose a serious risk when used in patients at risk for severe infections, including hospitalized patients. Healthcare-associated infections are estimated to occur in 5% of all hospitalizations in the United States. Additionally, these agents are used to induce remission of disease, not treat acute

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TNF-alpha restrictions?, from page 3

exacerbations. In the case of an acute exacerbation, patients can be treated with other agents that have a faster onset of action (eg, corticosteroids).

Infliximab, the only intravenously administered TNF-alfa inhibitor, was first reviewed by the P&T Committee in March 1999, when it was designated nonformulary and not available. The high cost was deemed too high for most inpatient reimbursement schemes and the onset of action was considered too slow. In September 2001, the P&T Committee re-evaluated infliximab and added it in the *Formulary*. It was restricted to approval by the Gastroenterology (GI) Division of the Department of Medicine. There was debate about the onset of action for Crohn's disease. In June 2007, the restriction for infliximab was lifted.

By 2007, infliximab was being used for several labeled (eg, rheumatoid arthritis) and off-labeled uses. It was no longer rational for the GI Division to approve this agent. A medication use evaluation was done to determine whether another form of restriction was needed. At that time, the use of infliximab was relatively low and mostly for Crohn's disease, other adult GI diseases, and for pediatric off-label

uses. Thus, because of the relatively low use, there was insufficient justification to institute another form of restriction. Data suggest that the use of infliximab at Shands at UF is now higher than at most comparable institutions.

Attending physicians who have evidence to support the continued availability of infliximab must submit their criteria for use and evidence to support these inpatient uses to hatton@ufl.edu by August 15, 2012. If there are specific instances that would justify nonformulary use of the subcutaneously administered TNF-alpha drugs (adalimumab, certolizumab, etanercept, and golimumab), these criteria and supporting evidence must also be submitted by August 15, 2012.

After these data are evaluated and independent searches of the literature done, a recommendation will be made to the P&T Committee for final action. This could happen as soon as September 2012. Those who submit criteria and evidence to support continued use will be invited to that meeting after they complete a Disclosure Form. Submissions with published evidence to support the use of these agents will have the most impact on the P&T Committee's final decision.

Drug information questions?

Contact the Drug Information Service



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Or submit your
question online at
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- All answers are thoroughly researched and referenced

For emergent questions that do not need thorough research, go to the pharmacy servicing your area.