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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 November 18, 2008. 7 drugs or dosage forms were added in the *Formulary* and 4 were deleted from the *Formulary*. 5 drugs or dosage forms were designated nonformulary and not available, 2 interchanges were approved, and 4 criteria for use were changed.

### ◆ ADDED

**Biotene® Moisturizing Mouth Spray** (by Laclede)*

**Automatically interchanged for Saliva Substitute*

**Collagenase Ointment** (Santyl® by Knoll)

**Levetiracetam Extended-Release** (Keppra® XR by UCB Pharma)

**Pentoxifylline** (Generic)

**Romiplostim** (Nplate™ by Amgen)†

*†Restricted to Nplate NEXUS restricted distribution program*

**SourceCF® Multivitamins** (by SourceCF)

**Ziprasidone Injection** (Geodon® IM by Pfizer)‡

*‡Restricted to the Psychiatry Service & cannot be used with other QT-prolonging agents*

### ◆ DELETED

**ADEK® Multivitamins** (by Axcan Scandipharm)§

*§Nonformulary and not available & changed to SourceCF®*

**Papain-Urea Ointment** (Accuzyme®)¶

**Phenylephrine 0.25% Nasal Drops & 1% Nasal Spray**

**Saliva Substitute** (Roxanne)¶

*¶Nonformulary and not available (removed from the market)*

*(continued on next page)*

POLICIES AND PROCEDURES

## Mandatory use of Transfer Medication Order Report

On November 20, 2008, the Medical Quality Committee approved the mandatory use of the *Transfer Medication Order Report* upon ALL transfers within Shands at UF. This requirement went into effect in December 2008. The *Transfer Medication Order Report* is available via NetAccess. This report lists all of the patient's currently active hospital medications, with check boxes to indicate if the medication should be continued or discontinued upon transfer. The completed form is an active order.

The *Transfer Medication Order Report* is already used by most physicians. This is likely due to the form's ease of use. Rather than rewriting each of the patient's medications, they are all printed on the form for the prescriber to either continue or discontinue.

The *Transfer Medication Order Report* was revised to include the following statement: "I have reviewed the patient's home medication list and current inpatient medication list, and have reconciled all discrepancies." Signing this order form indicates that the prescriber has reviewed and considered any home medications and current hospital medications that should be restarted or discontinued.

NEWS

## Verbal C-III update

On June 15, 2007, Florida Governor Crist signed HB 1155 amending existing law on the dispensing of controlled substances by a pharmacist. The law officially took effect on July 1, 2007.

The changes in the law were intended to help limit controlled substance diversion. One notable change involved verbal (eg, telephoned) Schedule III (C-III) prescriptions. This legal requirement can be found in the Florida Statutes Title XLVI Chapter 893.04(2)(e), which states, "A pharmacist may not dispense more than a 30-day supply of a controlled substance listed in Schedule III upon an oral prescription issued in this state."

Based on questions received in the Drug Information and Pharmacy Resource Center (DIPRC), there was controversy over the interpretation of this statute. Some pharmacists believed that the statute limits verbal C-III prescriptions to a single 30-day fill with no refills. Others believe that the phoned-in prescriptions can have up to the maximum legal limit of refills for Schedule III drugs (ie, 5 refills in 6 months) as long as each fill is restricted to a 30-day supply. Because of this ambiguity, the DIPRC petitioned the Board of Pharmacy for clarification.

At the June 10, 2008 meeting, the Board of Pharmacy tabled the issue to get the intention of the author of the bill passed by the legislature. Their preliminarily interpretation of the statute is to limit only the initial prescription to a 30-day supply (ie, no restriction on refills); however, this interpretation was not unanimous and required further clarification.

A final Declaratory Statement from the Board of Pharmacy dated September 19, 2008 states that it is the Board's opinion that this statute should be interpreted to mean that up to the maximum refills allowed by law can be dispensed, if the prescriber orally authorized refills for the prescription. However, each refill should be only a 30-day supply. Thus, phoned-in prescriptions for Schedule III controlled substances can be refilled up to the maximum of 5 refills in 6 months as long as each fill is restricted to a 30-day supply.

*References available upon request.*

### INSIDE THIS ISSUE

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◆ **NONFORMULARY AND NOT AVAILABLE**

**Granisetron Transdermal Patch** (Sancuso®)

**Phenylephrine 0.25% & 0.5% Nasal Drops and 1% Nasal Spray**

◆ **INTERCHANGES**

**Biotene® Moisturizing Mouth Spray** for **Saliva Substitute**

**SourceCF® Multivitamins** for **ADEK® Multivitamins**

◆ **CRITERIA-FOR-USE CHANGES**

**Coral Snake Antivenin** (by Wyeth)**

***Extended dating through October 2009*

**Epoprostenol** (Generic)††

*††Approved for inhaled use prior to nitric oxide*

**Methadone** (Generic)‡‡

*‡‡Restricted*

**Nitric Oxide** (INOmax®)§§

*§§Restricted*

**Biotene® Moisturizing Mouth Spray** was added in the *Formulary* to replace **Saliva Substitute**, which was removed from the market. The P&T Committee approved a therapeutic interchange that will allow Biotene® Moisturizing Mouth Spray to be dispensed for orders for saliva substitute.

Saliva substitutes are used for symptomatic relief of xerostomia. Xerostomia occurs in the elderly, patients on anticholinergic drugs, patients receiving radiation therapy, patients with Sjogren's syndrome, etc. The best treatment for xerostomia is to remove the cause, but measures like sugar-free gum or saliva substitutes may provide some comfort and/or prevent dental caries when the cause cannot be reversed. Biotene® Moisturizing Mouth Spray is sprayed into the mouth as needed.

**Collagenase ointment** was added in the *Formulary* to replace **Accuzyme® Ointment**, which was removed from the market after the FDA announced that papain-containing topical products are unapproved drugs and can no longer be sold after November 2008. Existing product could be used (ie, product was not recalled); however, our supplies of Accuzyme® will be exhausted by the end of December 2008.

Collagenase ointment is a sterile enzymatic debriding ointment containing collagenase in petrolatum. Its labeled indications include debriding chronic dermal ulcers and severely burned areas. Dermal ulcers include pressure ulcers (ie, decubitus ulcers), arterial ulcers, venous ulcers, and diabetic ulcers.

Collagenase is a naturally occurring enzyme found in human tissue. It is also produced by bacteria. Collagen accounts for approximately 75% of the dry weight of skin tissue. By breaking down collagen, collagenase promotes the separation of eschar from wounds. Collagenase ointment, which contains collagenase produced from the fermentation of Clostridium histolyticum, provides additional enzymes to promote the removal of eschar and the granulation of wounds. Collagen in healthy tissue or newly formed granulation tissue is not affected.

Adverse effects associated with collagenase ointment are limited to the area of application and include erythema, hyperemia, and local tissue damage. Hyperemia resulting from faulty application has been reported.

**Keppra® XR** is a new once-daily, extended-release (ER) dosage form of levetiracetam. Leviteracetam IV and immediate-release (IR) oral tablets and solution are already listed in the *Formulary.* Since there is no current recommended conversion between Keppra® XR and levetiracetam IR, this dosage form was added in the *Formulary*.

**Pentoxifylline** is a methylxanthine derivative that has been available in the US since 1984. It has a labeled indication for the treatment of intermittent claudication due to chronic peripheral arterial occlusive disease (PAOD). However, pentoxifylline is currently not recommended for PAOD. Despite its perceived lack of clinical utility, pentoxifylline has been frequently ordered for off-label indications.

Pentoxifylline is purported to provide beneficial immunologic and anti-inflammatory effects through the inhibition of tumor necrosis factor (TNF) synthesis. Based on prescribing patterns, the most common off-label use of pentoxifylline is for hepatic disease; TNF has been associated with the development of hepatitis.

The results of 2 studies demonstrate that pentoxifylline is beneficial in the treatment of hepatic disease. In a randomized controlled trial, pentoxifylline was found to decrease significantly the incidences of mortality and progression to hepatorenal syndrome in patients with acute alcoholic hepatitis. In a small uncontrolled trial, long-term treatment with pentoxifylline was associated with histological resolution of steatosis, inflammation, and fibrosis in patients with non-alcoholic steatohepatitis.

Reported adverse events in these studies were gastrointestinal disturbance and headache. The most frequently reported adverse effects in clinical trials are gastrointestinal disturbances (nausea, vomiting, and dyspepsia), dizziness, headache, and angina. Due to pentoxifylline's ability to decrease blood viscosity, patients on warfarin or with other risk factors for bleeding should be closely monitored.

**Romiplostim** is a thrombopoietin receptor agonist that has an FDA-labeled indication for the treatment of thrombocytopenia in patients with chronic ITP who have experienced inadequate response to other treatments. Romiplostim increases platelet production through activation of the thrombopoietin receptor, a mechanism like endogenous thrombopoietin.

Two randomized, double blind, placebo-controlled trials have evaluated the efficacy of romiplostim versus placebo in both splenectomized and non-splenectomized patients. The studies reported romiplostim effectively increased and sustained platelet counts while reducing the frequency of rescue medication use and concurrent therapy. An open-label extension study showed efficacy up to 96 weeks.

The most common adverse event reported was headache. Serious adverse reactions reported include the development or progression of reticulin fiber deposition within the bone marrow and worsening thrombocytopenia upon discontinuation of romiplostim therapy. Additional concerns are malignancy progression, possibility for thrombotic events, and the unknown significance of immunogenicity to romiplostim (and possibly thrombopoetin). Romiplostim has only been used in less than 300 patients for relatively short periods, so its safety in diverse patients for longer durations is not well-described.

Romiplostim is available only through a restrictive distribution program (Nplate™ NEXUS) that requires patients, prescribers, and the institution to be enrolled. Romiplostim is given once weekly as a subcutaneous injection; however, it requires that a healthcare provider administer the dose. The cost of romiplostim therapy is substantially higher than first- and second-line treatments; however, it is not indicated as a first- or second-line agent and is approved only for patients who have had insufficient results from other treatments.

Romiplostim was added in the *Formulary* and restricted to use in patients enrolled in its restricted distribution program when prescribed by prescribers (hematologists) enrolled in the restricted distribution program. Prescribers are responsible for reviewing the Nplate™ Medication Guide with the patient prior to each dose.

*(continued on next page)*

***Formulary update,*** *from page 2*

**SourceCF® multivitamins** replaced **ADEK® multivitamins** in the *Formulary*. ADEK® multivitamins have been designated nonformulary and not available and will be interchanged to SourceCF® multivitamins. ADEK® multivitamins have been chronically backordered; thus, SourceCF® multivitamins were selected as a close replacement.

These multivitamins are specially formulated for use in patients with cystic fibrosis who suffer from fat-soluble vitamin deficiencies as part of their disease (ie, poor fat absorption because of pancreatic insufficiency). Select other patients (eg, gastric bypass patients) may also take these specialty vitamins.

**Ziprasidone injection** was added in the *Formulary*, but was restricted to the Psychiatric Units (52PY and Vista) and is prohibited from concomitant use with other QT-prolonging drugs. The list of QT-prolonging drugs is quite extensive. A comprehensive list can be found at the University of Arizona's Center for Education and Research on Therapeutics (CERT) for QT-prolonging agents (ie, http://www.azcert.org/medical-pros/drug-lists/printable-drug-list.cfm).

Ziprasidone injection has a labeled indication for the management of acute episodes of agitation or acute psychosis (eg, hallucinations, delusions) in patients with acute exacerbations of schizophrenia. Haloperidol is the treatment of choice for acute psychosis secondary to schizophrenia. However, haloperidol is associated with extrapyramidal symptoms (EPS).

Two studies and a meta-analysis show that ziprasidone does not offer significant therapeutic benefits over haloperidol for acute agitation in psychotic patients. Although there is less risk for the development of EPS with ziprasidone, it may still cause these symptoms. Additionally, there are warnings of QT prolongation and increased death in dementia-related psychosis in the elderly.

The most common adverse effects for ziprasidone are somnolence, extrapyramidal symptoms, dizziness, akathisia, abnormal vision, nausea/vomiting, and headache. Ziprasidone use is contraindicated in patients with dementia-related psychosis, concomitant use of medications that may prolong QT interval, and congenital prolongation of QT interval. The contraindication with other drugs that prolong the QT interval is a major disadvantage for this product and significantly limits is usefulness.

**Phenylephrine 0.25% & 0.5% Nasal Drops and 1% Nasal Spray** were designated nonformulary and not available. The 0.25% and 0.5% of phenylephrine drops have been discontinued by its manufacturer. There are no alternatives on the market, and 1% phenylephrine drops remain in the *Formulary*. Phenylephrine 1% spray was deleted and designated it nonformulary and not available because it is not used. Phenylephrine 0.25% spray remains listed in the *Formulary*.

Phenylephrine is a topical alpha-1 adrenergic receptor agonist that causes vasoconstriction, which relieves congestion when applied as a spray or drop in the nose. Although phenylephrine has questionable efficacy when given orally, it is effective when applied to the nasal mucosa. Topical oxymetazoline nasal spray (Afrin®) is another topical nasal decongestant in the *Formulary*. Unlike topical nasal phenylephrine, which must be given every 4 hours, oxymetazoline spray is administered every 12 hours.

**Sancuso® transdermal patches** were designated nonformulary and not available, like all other forms of granisetron. Oral and injectable granisetron are automatically interchanged to ondansetron. Prescribers of granisetron patches will be contacted for a new order to convert to oral ondansetron tablets, an orally disintegrating ondansetron tablet (ODT), or injectable ondansetron. Like ondansetron, granisetron selectively blocks type 3 serotonin (5-$HT_3$) receptors. 5-$HT_3$ receptors are found centrally in the chemoreceptor trigger zone and peripherally at vagal nerve terminals in the intestines.

Transdermal granisetron patches need to be placed 24 hours in advance of their needed effect and have a labeled indication for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days duration. Oral and injectable ondansetron have a much faster onset of action.

**Coral snake antivenin** is used to treat patients with a significant envenomation from a coral snake bite. Unfortunately, the manufacturer stopped making this product several years ago, and the final supplies of product were scheduled to expire at the end of October 2008.

Based on stability data submitted to the FDA, a limited supply of coral snake antivenin (ie, Lot # 4030026) will have extended dating until the end of October 2009. Based on the limited number of vials on hand, it is unlikely that supplies will last until then. Once supplies are exhausted, coral snake antivenin will be designated nonformulary and not available. Unfortunately, there will be no pharmacologic treatment for coral snake bites once supplies are exhausted or after November 1, 2009.

**Epoprostenol** is identical to prostacyclin (also known as prostaglandin $I_2$), which occurs naturally in the body. Epoprostenol is a vasodilator and inhibits platelet aggregation. It is commercially available in an injectable dosage form and has a labeled indication as an intravenous infusion for the treatment of pulmonary hypertension in adults.

There are published data that show that inhaled epoprostenol has the same physiologic effects as inhaled **nitric oxide**; however, the onset of effect may be delayed. Because epoprostenol is available as a generic (and because of the amounts used), it is considerably less expensive than nitric oxide. For these reasons, restrictions on the use of nitric oxide will promote the off-labeled use of inhaled epoprostenol. Exceptions were established; when it is perceived that a delay in the effect of inhaled epoprostenol would make nitric oxide preferable.

Exceptions for the requirement of an epoprostenol (prostacyclin $I_2$) trial before the use of nitric oxide include: 1) pre- ECMO, PPHN, and CDH in the NICU; 2) rapid deterioration ($PaO_2$/$FIO_2$ less than or equal to 60); 3) pediatric post-operative cardiac surgery (per the Pediatric Cardiac Surgeons); 4) pulmonary hypertension (primary or secondary) with MPAP of 30 mm Hg or greater in the SICU/NSICU/CCU or 40 mm Hg or greater in MICU; 5) patients placed on a ventricular assist device (VAD); and 6) patients "who do not respond" to inhaled epoprostenol.

**Methadone** was restricted to specific uses because of concerns about its safety. Methadone is a potent synthetic opioid with complicated pharmacokinetic properties and pharmacodynamic effects that make it difficult to use. Methadone is often associated with opioid detoxification and maintenance, which are highly regulated and can be done only in DEA-registered treatment programs. However, since methadone is a "long-acting" opioid, it can be used for the treatment of pain, which is regulated like all other Schedule II controlled substances. Methadone has a black box warning in the official labeling that states methadone treatment for acute or chronic pain management should only be initiated if the potential benefits outweigh the risks.

Methadone use is difficult because there is wide patient-to-patient variation in its pharmacokinetics. Duration of effect becomes longer with prolonged use, and initial effects do not reflect the full effect of repeated doses. There are no reliable dosage

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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

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


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***Formulary update,*** *from page 3*
conversions to methadone from other opioids. These properties make initiation of therapy difficult.

The Pain Committee and the Medication Safety Committee recommended that methadone be restricted to ongoing treatment of opioid addiction, treatment of pediatric and adult opioid withdrawal symptoms, ongoing treatment of chronic and cancer pain, and initiation of chronic pain treatment by the Pain Service. A patient's methadone dose for chronic pain or methadone maintenance should not be changed. Methadone should not be used for acute pain. It will not be included in any pre-printed orders (unless it meets the above criteria). All orders for methadone must include the indication for use.

Florida statutes state that a patient can be maintained on a methadone maintenance program during their hospital stay if the patient is currently enrolled in a recognized methadone maintenance program. The status of the patient in a methadone program must be verified for that patient, and the status will be documented in the chart before continuing therapy while the patient is hospitalized for another reason.

**NEWS**

# P&T Committee Actions 2008

Another year of Pharmacy and Therapeutics (P&T) Committee activity was just completed. During this time, the Committee met 10 times. The goals of the Committee are to use evidence-based medicine principles to establish drug use policies and to establish a formulary. In addition, medication safety is promoted.

The P&T Committee is a medical staff committee that is the formal line of communications between the medical staff and Shands at UF as it relates to all drug-related matters. Currently, 14 medical staff members help decide which drugs are readily available for use, what limitations should be put on those drugs that are available, and what can be done to improve medication safety. Members of the P&T Committee are appointed by the Chief of Staff.

The *Formulary* is a list of drugs that are readily available for use. Drugs listed in the *Formulary* can be found on the Shands Portal at http://shandsformulary.shands.ufl.edu. This database of drugs listed in the *Formulary* requires a portal username and password, if you are not logged onto the portal.

Last year, 38 new products were added in the *Formulary*. Only 11 new drugs were requested, the rest of the additions were proactive actions taken by the P&T Committee. 18 drugs were deleted from the *Formulary.*

57 drugs were reviewed by the P&T Committee and designated nonformulary and not available; 11 of these products have been removed from the market. These medications cannot be obtained through a nonformulary request.

Several drug use policies were approved. Therapeutic interchange changes, IV-to-oral conversions, physician-approved protocols, and restriction changes were approved. Actions to improve medication safety were emphasized.

The *Drugs & Therapy Bulletin* (now beginning its 23nd year of publication) remains the primary method for communicating P&T Committee actions. Please take the time to read the changes that occur each month. Back issues of the *Bulletin* are available on the Internet at http://www.shands.org/professionals/drugInfo/bulletin.asp.