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B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met May 20 and June 17, 2014. 5 drugs were added in the *Formulary*, 4 drugs were deleted, 1 drug was designated non-formulary high priority, 2 drugs had criteria for use changes, and 1 temporary therapeutic interchange was approved.

◆ ADDED

Alemtuzumab (Campath®)*

**Restricted to use in solid organ transplantation for the prevention of acute rejection or for chronic lymphocytic leukemia in patients who have failed other regimens.*

Cisatracurium (Nimbex®)*

**Restricted to use in the ICU for the treatment of acute respiratory distress syndrome (ARDS) in association with a developed protocol.*

Entecavir (Baraclude®)

Gadoterate meglumine (Dotarem®)

Saline nasal gel (Ayr Gel®)

◆ DELETED

Boceprevir (Victrelis®)

Gadobenate dimeglumine (MultiHance®)

Hypromellose 1.5% (Isoptotears®)

Telaprevir (Incivek®)

◆ HIGH-PRIORITY NON-FORMULARY

Miltefosine (Impavido®)*

**Restricted to approval by Infectious Diseases for the treatment of leishmaniasis and amebiasis.*

◆ CRITERIA FOR USE CHANGES

Dexmedetomidine (Precedex®)*

**Added restriction for use to prevent intubation in patients with alcohol withdrawal as part of an approved protocol.*

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PHYSICIAN COMMENTARY REQUESTED

FDA Removes High-dose Acetaminophen in Combination Products

Prescription combination drug products containing acetaminophen, and often an opioid, account for approximately 20% of the total acetaminophen drug market.[1] These combination drug products are FDA-approved for moderate to severe pain and are commonly prescribed for acute injuries, operations, and dental procedures.[2] Opioids are central nervous system (CNS) mu-receptor agonists which alter the perception of response to pain via inhibition of the ascending pain pathways, while acetaminophen has been postulated to work by inhibition of the synthesis of prostaglandins in the CNS and blockage of peripheral pain impulse generation.[3-4] Acetaminophen is generally considered safe at therapeutic doses, but could be potentially fatal with doses greater than the FDA-recommended daily amount of 4,000 mg.[5] Exceeding the recommended dose may cause liver injury resulting in liver failure, need for liver transplant, or death.

Acetaminophen-induced liver injury is caused by a toxic intermediate metabolite, N-acetyl-p-benzoquinone imine (NAPQI), that is produced when acetaminophen is metabolized via cytochrome P4502E1.[6-7] At therapeutic doses of acetaminophen, NAPQI combines with intracellular glutathione to become a non-toxic derivative and is excreted in the urine. High doses of acetaminophen can lead to increased production of NAPQI, which can deplete glutathione stores. As a result, the body is unable to detoxify the excess NAPQI, which binds to liver proteins and causes mitochondrial cell injury and destruction of hepatocytes.[6,8]

Acetaminophen overdose has become the leading cause of acute liver failure (ALF) as well as a leading cause of death from ALF in the United States.[9] Data collected from four surveillance systems revealed approximately 56,000 emergency room visits, 26,000 hospitalizations, and 458 deaths per year related to acetaminophen overdoses during the 1990s.[10] According to the National Poison Data System (NPDS), 30% (41,999/138,602) of all acetaminophen-associated calls to poison centers in 2005 involved prescription acetaminophen combination products. Additionally, these products were involved in approximately 44% (1,470/3,310) of acetaminophen-associated calls that resulted in serious injury and 48% (161/333) of acetaminophen-associated calls that resulted in fatalities.[11]

Cases of severe liver injury or fatalities involving acetaminophen have often occurred in patients who took more than the prescribed dose of an acetaminophen-containing product over a 24-hour period, who took more than one acetaminophen-containing product at the same time, or who consumed alcohol concurrently with acetaminophen products.[12] Consumption of more than the prescribed dose may be attributed to lack of patient awareness of the many acetaminophen-containing prescription and over-the-counter (OTC) products. In addition, the Tylenol® website failed to list acetaminophen as an ingredient or abbreviated acetaminophen as APAP on medication container labels adding to patient confusion.[12-13] Omissions and abbreviations which may be difficult for patients to understand, occur due to the size and space limitations of both inventory fields in computers and on pharmacy labels. Furthermore, many pharmacies have deactivated the duplicate checking function for drugs in the same therapeutic class secondary to excessive alerts potentiating alert fatigue, thus reducing the ability to warn staff about excessive acetaminophen doses.[12] With regard to outpatient use, manufacturers of OTC

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Formulary update, *from page 1*

Prothrombin Complex Concentrate (Kcentra®)*

**Added restriction for anticoagulation reversal in patients receiving warfarin with an INR >1.7 who require emergent procedural intervention (i.e. within 6 hours).*

◆ THERAPEUTIC INTERCHANGES

Cefotetan to Cefoxitin*

**Temporary interchange secondary to national shortage of cefotetan*

Alemtuzumab was originally added in the *Formulary* in 2001 for patients with chronic lymphocytic leukemia (CLL) who had failed alternative therapies. In April 2013, alemtuzumab restrictions were changed to allow for the use of alemtuzumab for the prevention of rejection (induction therapy) in solid organ transplant patients. Both indications require utilization in accordance with the Campath Distribution Program. At that time, alemtuzumab was designated Non-Formulary High-Priority as the medication had to be ordered on a patient-specific basis and could not be regularly stocked.

In recent months, changes in the Campath Distribution Program have occurred. UF Health is now given an annual allotment of alemtuzumab in accordance with the prior year's utilization. These vials may be utilized in a non-patient-specific manner for either CLL or prevention of rejection in solid organ transplant patients. Once the allotment runs out, alemtuzumab may only be ordered on a patient-specific basis. At this time, indications outside these criteria require approval by the medical board in the Campath Distribution Program as well as Pharmacy Administration on Call.

Based upon these data, the Pharmacy and Therapeutics Committee recommended adding alemtuzumab in the *Formulary* restricted to prevention of acute rejection in solid organ transplant recipients and for patients with CLL who have failed alternative therapies. All additional uses of alemtuzumab will require pharmacy administration on-call approval as well as approval from the Campath Distribution Program.

Cefotetan is currently unavailable secondary to a national shortage. As the need for cephalosporin alternative therapy exists, a proposal was made to interchange cefotetan to cefoxitin temporarily during this shortage. Of note, most recent estimates indicate the shortage is unlikely to resolve until late fall 2014.

Infection Severity	Cefotetan	Cefoxitin
Moderate to Severe	1-2gm IV q8-12 hours	1-2gm IV q6 hours
Life-Threatening	3gm IV q8-12 hours	2gm IV q4 hours
Surgical Prophylaxis Pre-Op	2gm IV x1 dose	2gm IV x1 dose
Surgical Prophylaxis Post-Op	2gm IV q8 hours x2 doses	2gm IV q6hours x3 doses

Cisatracurium was reviewed for the use in acute respiratory distress syndrome (ARDS). In a multicenter, double-blind, placebo-controlled trial 340 patients who presented to the intensive care unit with ARDS were randomized to receive either cisatracurium or placebo for 48 hours. Patients in this study were ventilated with standard lung-protective mechanical ventilation and bolus followed by a continuous infusion of cisatracurium or placebo for 48 hours.

After adjustment for baseline PaO_2:FiO_2 ratio, SAPS II score, and plateau pressure, the hazard ratio for death at 90 days in the cisatracurium group, as compared with the placebo group, was 0.68 (95% CI, 0.48 to 0.98; p=0.04). In subgroup analysis, patients who presented with a PaO_2:FiO_2 ratio of less than 120, the 90-day mortality rate was 30.8% in the cisatracurium group compared to 44.6% in the control group (p=0.04). However, no differences in mortality were observed at 28 days between patients who received cisatracurium or placebo (23.7% vs. 33.3%; p=0.05).

Patients who received cisatracurium had significantly more ventilator-free days than the placebo group during the first 28 and 90 days of the study (10.6 + 9.7 vs. 8.5 + 9.4; p=0.04 and 53.1+35.8 vs. 44.6+37.5; p=0.03, respectively), days outside the ICU during the first 90 days of the study (47.7+33.5 vs. 39.5+35.6; p=0.03), less barotrauma (9 vs. 19 patients; p=0.03) and a lower incidence of pneumothorax (7 vs. 19 patients; p=0.01). There was no difference in the number of patients who developed paresis by day 28 or ICU discharge (p=0.64 and p=0.51, respectively).

In January 2014, the Formulary Subcommittee recommended that cisatracurium be added in the *Formulary* restricted to intubated patients with a diagnosis of ARDS as part of a developed ARDS protocol. The P&T Committee agreed with this recommendation and voted to approve the addition in the *Formulary* pending the development of an ARDS protocol.

A protocol was developed in conjunction with medical, surgical, and pharmacy staff. Input from nursing and respiratory therapy was sought as well. This protocol was presented to the Committee for approval. It was suggested that a PaO_2:FiO_2 ratio of <150 mmHg may be an appropriate target for intervention and easier to operationalize in the critically ill patient population. This target range closely mimics the enrollment population in the study and allows for earlier intervention which may decrease the use of other high-cost therapies including nitric oxide and/or epoprostenol.

The Pharmacy and Therapeutics Committee agreed with the construction of the protocol and approved the use of cisatracurium in patients with ARDS in the ICU who have a PaO_2:FiO_2 ratio of <150 mmHg. In addition, ordering of cisatracurium will be limited to Attending Physician or Fellow Physician. Prospective evaluation of adherence to criteria by the verifying pharmacist is required.

Dexmedetomidine was reviewed by the Pharmacy and Therapeutics (P&T) Committee for addition to the *Formulary* in 2002, 2004, 2008, and for use in pediatrics in 2010. Dexmedetomidine was added to the *Formulary* with restrictions in 2008 based on evidence for use in awake craniotomy, awake intubation, ventriculostomy placement for non-intubated patients, and transition to extubation for agitated patients who are difficult to wean from the ventilator. In 2010, dexmedetomidine was approved for use in pediatrics with restrictions outlined in the Pediatric Dexmedetomidine Order Set.

A medication-use evaluation in 2009 revealed modest use of the product at UF Health Shands Hospital, an average of 8 administrations per month, primarily for awake intubation. In 2012, dexmedetomidine was evaluated for four possible criteria additions: opioid-sparing effects in hospitalized non-OR patients, opioid-sparing effects in OR, opioid-sparing effects in post-surgical patients and primary analgesia in OR patients on buprenorphine where opioids are contraindicated or less effective. The Committee approved use

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Formulary update, *from page 2*

in the OR for patients who were not responding to opioids or who were receiving buprenorphine.

An interest in expanding the current criteria for use for up to 24 hours to prevent intubation and mechanical ventilation in agitated patients who are withdrawing from alcohol or other substances as a bridge to other pharmacotherapies (clonidine and beta-adrenergic antagonists) was approved as an additional criteria in January 2014, pending the development of an alcohol withdrawal protocol.

In June 2014, an ICU alcohol withdrawal algorithm was presented which incorporates dexmedetomidine specifically for prevention of intubation in alcohol withdrawal syndrome (AWS) patients. It was proposed that as part of the protocol, dexmedetomidine be utilized with the following parameters:

- ICU setting only *AND*
- Patient is not currently intubated *AND*
- Receipt of > 16 mg lorazepam in 4 hours OR > 40 mg lorazepam in 24 hours *AND*
- Symptoms of uncontrolled withdrawal/ RASS > 3 *AND*
- SPO_2 < 92, RR < 10, or RR >24

The verifying pharmacist is responsible for proactively ensuring these criteria are met prior to initiation of therapy. In addition to these parameters, alternative therapies, including but not limited to propranolol and clonidine were required to be initiated, if not already active on profile. Dexmedetomidine must be written by an attending physician and be subject to the 24-hour expiration time.

The Pharmacy and Therapeutics Committee agreed with the construction of the protocol and approved the use of dexmedetomidine in conjunction with the above described protocol.

Entecavir is a guanosine nucleoside analogue with activity against hepatitis B virus (HBV) reverse transcriptase. It was FDA-approved in 2005 for treatment of chronic HBV infection in adults and children at least 2 years of age with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. In 2011, the European Associations for the Study of Liver Disease (EASL) noted the use of entecavir prophylaxis without hepatitis B immunoglobulin (HBIG) may be safe and effective in preventing HBV recurrence post-liver transplantation. Additionally, the 2012 American Association for the Study of Liver Diseases (AASLD) and the American Society of Transplantation recommend the use of antiviral therapy with or without HBIG depending on the basis of transplant clinical and virological characteristics. There is no consensus about the optimal antiviral regimen for HBV prophylaxis in post-liver transplantation.

Currently, entecavir and tenofovir are considered first line agents for treating HBV infection in both non-cirrhotic and cirrhotic patients due their enhanced antiviral activity, excellent side-effect profile, and high barriers to resistance. Efficacy and safety data are limited on the use of entecavir as monotherapy for HBV prophylaxis in post-liver transplant patients as most studies used entecavir plus hepatitis B immune globulin (HBIG). Data suggest that entecavir is safe and effective at preventing HBV recurrence in post-liver transplant patients although most studies failed to include a control group and had both variable HBIG use and variable baseline serum HBV deoxyribonucleic acid (DNA) level at time of transplant.

Entecavir carries a boxed warning cautioning clinicians to be mindful of the risk for lactic acidosis and severe hepatomegaly with steatosis, especially in the HIV co-infected patient. Additionally, in patients with chronic HBV, severe acute exacerbations of hepatitis B may occur upon discontinuation of anti-HB therapy, including entecavir. Finally, patients co-infected with HIV should not use entecavir unless also receiving highly active antiretroviral therapy (HAART).

Following a review of the literature, entecavir in combination with HBIG is deemed effective for HBV prophylaxis in post-liver transplant patients as evidenced by rapid reductions in HBV DNA levels post-liver transplant. Additionally there is demonstrated efficacy for entecavir monotherapy as HBV prophylaxis post-liver transplant by reducing HBV DNA levels and maintaining HBsAg seroclearance when compared to other antiviral therapies. Based on these reports, EASL and AASLD have identified that entecavir plays a positive role in HBV treatment in patients with or without a liver transplant.

In review of adverse events and cost, entecavir is well tolerated (fewer patients may develop nephrotoxicity) and is cost neutral compared to tenofovir. Based on this information tenofovir will remain our first-line agent for HBV management post liver transplant. Due to its potential safety benefit, it was recommended that entecavir be added into the *Formulary* for HBV therapy in liver transplant recipients who are receiving 2 or more nephrotoxins or are experiencing acute kidney injury at the time of treatment initiation. The Pharmacy and Therapeutics Committee agreed with this recommendation. The Committee also voted to delete **boceprevir** and **telaprevir** in accordance with Anti-Infective Subcommittee recommendations. These removals are secondary to newer agents available and lack of use.

Gadoterate meglumine is a macrocyclic and ionic gadolinium-based contrast agent (GBCA) intended for magnetic resonance imaging (MRI) diagnostic examinations. It has seven unpaired electrons in the gadolinium ion Gd3+ which produce the paramagnetic activity. When used in a magnetic field, gadolinium ions increase signal intensity (brightness) of tissues by shortening relaxation times of water protons in blood and tissues, and therefore improve visualization of normal and pathological tissues.

Gadoterate meglumine has a comparable diagnostic efficacy to other gadolinium-containing contrast media in MRI examinations of the central nervous system (CNS). In randomized, double-blind clinical trials comparing Gd-DOTA (Dotarem®) to Gd-DTPA (Magnevist®), no difference was found in the diagnostic benefits between the two contrast agents. Contrast-enhanced MR images did not affect diagnostic efficacy although it did ease the therapeutic decision by improving image qualities.

Gadoterate meglumine has a safety profile similar to other GBCAs. Most adverse events are transient, self-resolving, and mild in severity. The most commonly described adverse reactions were nausea, headache, injection site pain, injection site coldness, and burning sensation.

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Formulary update, *from page 3*

Post-marketing observational studies showed that the overall incidence of immediate/acute adverse reactions after injection was less than 1%, ranging from 0.34 to 0.93%. The most serious adverse effect associated with the use of GBCAs is nephrogenic systemic fibrosis (NSF) which is a severe delayed fibrotic reaction of the body tissues to some gadolinium-based contrast media that occurs in patients with severe renal impairment (defined as GFR < 30 mL/min/1.73m^2). Insufficient evidence is available to differentiate between the GBCAs with respect to the risk of NSF although all gadolinium-based products carry a black box warning describing the risk. Theoretically, gadoterate meglumine has the least gadolinium-associated toxicity potential secondary to its unique chemical structure which demonstrates the highest thermodynamic and kinetic stability among the GBCAs. The macrocyclic chelates where Gd3+ is caged offers a better protection in comparison to the linear structure, thus minimizes the amount of toxic gadolinium ions which are released. Over 37 million doses of gadoterate meglumine have been administered since its initial approval in 1989, with no confirmed case of NSF attributed to gadoterate meglumine when used exclusively without any other GBCAs in a patient. It is postulated that a very low risk of NSF is anticipated for gadoterate meglumine use.

The Pharmacy and Therapeutics Committee voted to add gadoterate meglumine in the *Formulary* and remove **gadobenate dimeglumine (MultiHance®)** and designate it Non-Formulary and Not Available. No changes to current practices with regards to utilization of contrast in patients with creatinine clearance <30 mL/min or acute kidney injury will occur. Use of contrast may be considered when expected diagnostic benefit of a gadoterate meglumine-enhanced MRI examination and its significance for therapeutic decision-making clearly outweigh the risk of an adverse event in a patient with kidney dysfunction. Current stores of gadobenate dimeglumine will be utilized prior to the switch.

Hypromellose 1.5% ophthalmic solution was identified as a redundant ophthalmic lubricant as polyvinyl alcohol 1.4% is also available in the *Formulary*. Hypromellose was deleted in the *Formulary* to correct this redundancy.

Miltefosine is a recently approved antimicrobial agent indicated for the treatment of *leishmaniasis*. This is the first oral agent approved for this indication. Although FDA approval is limited to *leishmaniasis*, there is also data supporting its utilization in amoebic encephalitis secondary to Free-Living Amoebas (FLA). Penetration into cerebral parenchyma and cerebrospinal fluid in combination with minimal toxicities create a desirable therapeutic profile for this medication.

The Pharmacy and Therapeutics Committee, in conjunction with the Anti-Infective Subcommittee, voted to designate this agent non-formulary, high priority with use restricted to approval by Infectious Diseases for the treatment of *leishmaniasis* and *amebiasis*.

Prothrombin Complex Concentrate (Kcentra®)is a four-factor prothrombin complex concentrate (PCC) originally approved by the Food and Drug Administration (FDA) in April 2013 for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonists (VKA) in adult patients with acute major bleeding. In late 2011, due to the potential risks associated with factor product administration, the Pharmacy and Therapeutics (P&T) Committee established criteria for use for PCC. Use is currently restricted at UF Health Shands Hospital for patients receiving warfarin with an International Normalized Ratio (INR) >1.7 who present with a life-threatening hemorrhage.

An ongoing medication use evaluation (MUE) has revealed an increase in the use of PCC for indications outside of its established criteria for use, specifically in patients requiring urgent surgery or invasive procedures. In December 2013, the FDA granted approval for urgent reversal of acquired coagulation factor deficiency induced by VKA therapy in adult patients needing an urgent surgery or other invasive procedure. The MUE findings along with the recent change in FDA-approved indications have prompted a re-review of PCC.

The administration of PCC rapidly increases plasma levels of the vitamin K-dependent coagulation factors II, VII, IX, and X as well as anticoagulant proteins C and S. It is recommended to measure the INR before treatment and then individualize dosing based on the INR value and the patient's body weight. The 2012 Antithrombotic Therapy and Prevention of Thrombosis (CHEST) guidelines do not address the use of PCC for VKA reversal as they were published prior to the 2013 expansion of the FDA-approved indication for Kcentra®. However, the British Committee for Standards in Haematology (BCSH) recommends four-factor PCC for urgent anticoagulation reversal in patients on warfarin requiring an emergent surgery which cannot be delayed for 6-12 hours.

Kcentra® is marketed under different trade names, Beriplex® P/N and Confidex® in various countries, where it has been used and studied in regards to efficacy and safety for urgent reversal of VKA in patients requiring urgent surgery or invasive procedures. Data suggests that four-factor PCC is effective at reversing VKA-associated coagulopathy more rapidly than fresh frozen plasma (FFP) in patients who require urgent surgery or invasive procedures. However, most studies were underpowered for measuring bleeding outcomes and some enrolled non-surgical patients, evaluated surrogate markers such as INR normalization, and failed to include a control group with FFP.

The most serious adverse events seen with PCC are thromboembolic events. The prescribing information for this product includes a black box warning due to this risk. However, the results of a pharmaco-vigilance study that evaluated the events reported over a 16-year period showed that the risk of these thromboembolic events is low.

PCCs have been demonstrated to establish hemostasis and achieve the pre-defined target INR in a specified timeframe. One study conducted by Refaai et al has shown superiority in regards to achieving the predefined target INR and hemostatic efficacy compared to FFP.

Despite an increased cost and limitations to current studies, the advantages of Kcentra® support the expanded criteria for patients receiving warfarin, with an INR of >1.7 who require an emergent procedural intervention within 6 hours. Documentation in the medical record should indicate why the procedure was deemed emergent. Continued evaluation of use will occur within 24-48 hours of all administered doses. The

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Formulary update, *from page 4*

Pharmacy and Therapeutics Committee voted to approve this expansion of the criteria.

Saline nasal gel (Ayr Gel®) was requested for utilization at Florida Surgical Center (FSC) for ENT procedures. Otolaryngology utilizes ArthroCare® ENT reflex 45 plasma wands during surgical procedures. These wands must be dipped in saline gel to create a conductive media required for the procedure at hand. The Pharmacy and Therapeutics Committee voted to approve the addition of saline nasal gel in the *Formulary*.

Acetaminophen combination, *from page 1*

drugs are required by law to list all the active ingredients of OTC drugs on the package label. However, the ingredients in some products, including those with brand name extensions, remain unclear for some patients. The Federal Trade Commission (FTC) does not require OTC drug advertisements to contain a list of all active ingredients.[12]

In January 2011, the FDA recommended that healthcare professionals discontinue prescribing and dispensing prescription combination drug products containing more than 325 mg of acetaminophen per dosage unit. This was done in an effort to protect patients from acetaminophen-induced livery injury caused by unintentional acetaminophen overdose. The FDA noted the absence of data showing that taking greater than 325 mg of acetaminophen per dosage unit provides additional benefit that outweighs the added risks of liver injury. At the same time, the FDA asked manufacturers of prescription acetaminophen combination drug products to limit the amount of acetaminophen to no more than 325 mg in each dosage unit by January 14, 2014.[2] More than half of manufacturers voluntarily complied.

The FDA recommends that pharmacists contact prescribers to suggest limiting acetaminophen to no more than 325 mg per dosage unit.[14] If prescribers are unwilling to modify their prescriptions, unfortunately, there is no clear guidance at this time.

To address these issues, some hospitals have restricted prescription combination products with higher amounts of acetaminophen.[12] UF Health Shands Hospital inpatient medication *Formulary* contains oral, rectal, and intravenous forms of single-agent acetaminophen. The *Formulary* also contains combination opioid / acetaminophen products such as acetaminophen/oxycodone tablets (Percocet®) and oral liquid (Roxicet®). These medications may either be ordered as "scheduled" or "as needed (PRN)" medications. Additionally, patients may have more than one of these products ordered at a time since many times they are ordered "as needed" for either pain or fever. The FDA's focus on safety of acetaminophen-containing combination products along with concern for accidental overdoses of hospitalized patients receiving acetaminophen through multiple products prompted the Medication Safety Committee, the Pain Committee, and the Pharmacy and Therapeutics Committee to recommend removal of all combination acetaminophen products from the *Formulary* (with the exception of Fioricet®, since the individual components of this medication are not available as single agents).

Because these medications have historically been widely used, the Pharmacy and Therapeutics Committee is seeking comment either in support or dissent of this proposed formulary action, with rationale to support the opinion. **Please submit your comments to Amy Rosenberg, PharmD Medication Safety Specialist at roseaf@shands.ufl.edu by August 8, 2014.**

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EDITOR, DRUGS & THERAPY BULLETIN
Carrie A. Lagasse, PharmD

DIRECTOR, PHARMACY SERVICES
Thomas E. Johns, PharmD

CHAIRMAN, PHARMACY & THERAPEUTICS COMMITTEE
I. David Weiner, MD
Professor of Medicine and Physiology and Functional Genomics
University of Florida, College of Medicine

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