

MEDICATION SAFETY IN SECONDS

A MONTHLY PUBLICATION FROM VA MEDSAFE:
VA'S COMPREHENSIVE PHARMACOVIGILANCE CENTER

Helping to achieve safe medication use

IMPORTANT CHANGE WITH HEPARIN LABELS

A National Alert Network (NAN) Alert issued in June 2013 reported a fatal heparin overdose associated with label confusion. A patient erroneously received 30,000 units (3 vials) of heparin instead of 3,000 units because the nurse and the medical student misinterpreted that each 10 milliliter (mL) vial contained 1,000 units of heparin when in fact, the vial held 10,000 units (Figure 1). The patient developed intracranial hemorrhage and brain stem herniation, followed by death.



Figure 1. Vials and labels for heparin 10,000 units misinterpreted as 1,000 units. SOURCE: NAN ALERT, June 2013.

This incident comes at the heels of the new USP label standard for heparin, which went into effect on May 1, 2013. During the transitional period where vials displaying the old label and vials displaying the revised label are both in circulation, there may be a great

er risk of confusing the amount per mL depicted on the older label as the total amount in the vial. New heparin vial labels state the total amount in units per the entire volume within the container followed by the unit strength per mL in parentheses (Figure 2).



Figure 2. New Heparin USP Label Standard.

Within the VA, the following steps have been recommended by pharmacy leadership to help ensure a smooth transition and safeguard against potential error:

- Ensure pharmacy staff engaged in ordering, dispensing, and preparing heparin products are aware of the labeling change.
- Store “current” and “revised” heparin in separate areas of the pharmacy.
- Ensure stock is not mixed together in patient care areas and only one product label is available in any ward/clinic stock areas.
- Consider signage in all areas where heparin is stocked.
- Educate ALL staff involved in procurement, storage, ordering, dispensing, and

IN THIS ISSUE:

- ▶ IMPORTANT CHANGE WITH HEPARIN LABELS.....1,4
- ▶ MEDICATION SAFETY NEWS FROM THE VA NATIONAL PHARMACY BENEFITS MANAGEMENT SERVICES [PBM] AND THE FOOD AND DRUG ADMINISTRATION [FDA].....2,4
- ▶ SAFETY CONSIDERATIONS WITH THE USE OF SODIUM PHOSPHATE/ SODIUM BIPHOSPHATE ENEMAS.....3



VA PHARMACY BENEFITS MANAGEMENT SERVICES (PBM)

PBM maintains VA's national drug formulary, as well as promotes, optimizes, and assists VA practitioners with the safe and appropriate use of all medications.

VA CENTER FOR MEDICATION SAFETY (VA MedSAFE)

VA MedSAFE performs pharmacovigilance activities; tracks adverse drug events (ADEs) using spontaneous and integrated databases; enhances education and communication of ADEs to the field; and promotes medication safety on a national level.

EDITOR-IN-CHIEF

Marie Sales, Pharm.D.
VA Pharmacy Benefits Management Services [PBM] & Center for Medication Safety [VA MedSAFE]; 1st Avenue—1 Block North of Cermak Road | Building 37; Room 139 | Hines, Illinois | 60141; www.pbm.va.gov

(continued on page 4)

from the pbm

- Medtronic Recall of Reservoirs Used with Paradigm Insulin Pumps Due to Leaks – 07/23/2013 – [National PBM Communication](#)
- Hydroxyethyl Starch Solutions and Mortality and Acute Kidney Injury – 07/19/13 – [National PBM Bulletin](#)
- ASA Lot Recalled for Containing APAP Instead – 07/01/13 – [National PBM Communication](#)

INFECTIOUS DISEASES

[FDA Drug Safety Communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects](#)

7/29/2013

Neurologic and psychiatric side effects associated with the antimalarial drug mefloquine hydrochloride has brought about the addition of a new boxed warning to the drug label. Neurologic side effects include dizziness, loss of balance, tinnitus, or vertigo; psychiatric side effects can involve feeling anxious, mistrustful, depressed, or having hallucinations. FDA reviewed adverse event reports from the FDA Adverse Event Reporting System (FAERS) and the published literature and found that:

- Symptoms can occur at any time during mefloquin use, and has developed sometimes after one or two doses.
- Neurologic and psychiatric symptoms persisted for months to years after discontinuation of mefloquine, and resulted in permanent vestibular damage in some cases.

[FDA Drug Safety Communication: FDA limits usage of Nizoral \(ketoconazole\) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems](#)

7/26/2013

FDA has approved label changes and added a new Medication Guide to:

- **Limit ketoconazole oral tablet use**
 - The use of ketoconazole tablets in *Candida* and dermatophyte infections is no longer indicated. Nizoral tablets should be used only when other antifungal drugs are not available or tolerated by the patient [*Boxed Warning, Warnings, Precautions, and Indications and Usage* sections].
 - Nizoral tablets are indicated only for the treatment of the following fungal infections: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis in patients in whom other treatments have failed or who are intolerant to other therapies [*Indications and Usage* section].
 - Nizoral tablets are not indicated for the treatment of fungal infections of the skin or nails.
- **Warn that ketoconazole oral tablets can cause severe liver injuries and adrenal gland problems**
 - Nizoral tablets should not be used in patients with acute or chronic liver disease [*Contraindications* section].
 - New assessment and monitoring recommendations for evaluation of hepatotoxicity should be followed [*Boxed Warning, Warnings, and Precautions* sections].
 - Assess the liver status of the patient before starting oral ketoconazole, with baseline laboratory tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, prothrombin time, and international normalized ratio (INR).
 - While the patient is taking oral ketoconazole, serum ALT should be monitored weekly for the duration of treatment. If ALT values increase to a level above the upper limit of normal or 30 percent above baseline, or if the patient develops symptoms of abnormal liver function, ketoconazole treatment should be interrupted and a full set of liver tests should be obtained. Liver tests should be repeated to ensure normalization of values.
 - Hepatotoxicity has been reported with restarting of oral ketoconazole.
 - Do not use Nizoral tablets in patients with underlying liver disease.
 - Other hepatotoxic drugs and alcohol should be avoided while taking Nizoral tablets.
 - Adrenal function should be monitored in patients with adrenal insufficiency or with borderline adrenal function and in patients under prolonged periods of stress (major surgery, intensive care, etc.) [*Warnings* section].

NEWSWORTHY...

from the fda

(continued on page 4)

Getting the most from our safety surveillance

SAFETY CONSIDERATIONS WITH THE USE OF SODIUM/PHOSPHATE/SODIUM BIPHOSPHATE ENEMAS

In the VA, sodium phosphate/sodium biphosphate enema is available for bowel preparation prior to a procedure or for intermittent management of constipation. On March 26, 2013, the PBM VA Center for Medication Safety issued a [National PBM Bulletin](#) in response to a fatality in a patient with severe constipation who had been prescribed, and who received, several sodium phosphate/sodium biphosphate enemas in less than 12 hours. Reports of severe adverse events resulting in severe electrolyte imbalance (hypernatremia, hyperphosphatemia, hypocalcemia, hypokalemia), dehydration and hypovolemia, tetany, QT prolongation, seizures, coma, and death are rare, but have been reported in the literature. An increased risk for severe adverse events or mortality may be associated with gastrointestinal disorders

CONTRAINDICATIONS

- Constipation in patients aged ≥ 70 years
- Congestive heart failure
- Clinically significant impairment of renal function (eGFR < 30 ml/min)
- Known or suspected gastrointestinal obstruction
- Megacolon (congenital or acquired)
- Paralytic ileus
- Perforation
- Active inflammatory bowel disease
- Imperforate anus
- Dehydration
- Generally, in cases of increased absorption capacity or decreased elimination
- Hypersensitivity to any product ingredients

In addition, the following safety consideration for dosage and administration are noted:

- Administration of more than one enema in 24 hours, particularly in patients with constipation, risk factors for electrolyte disturbances and comorbidities, can be harmful and has resulted in death.
- In those cases where complications have been reported, overdoses are often involved.
- No other sodium phosphates preparation including sodium phosphates oral solution or tablets should be given concomitantly.
- Use of sodium phosphate enemas for chronic management of constipation is not recommended. If an enema is indicated for management of severe constipation (after alternate treatment options have been attempted), consider using warm water enemas or mineral oil enemas (i.e., following disimpaction) before considering sodium phosphate enemas. These treatments may have the potential for toxicity if not used appropriately, with recommendations not to exceed more than one per 24 hours. If a sodium phosphate enema is used for severe constipation, it is recommended that no more than one dose be administered per 24 hour period, for no more than 3 days.

causing increased retention of enema contents in the gut; in addition, risks also include chronic renal failure, advanced age, and number of doses administered exceeding one within 24 hours.

In an effort to increase awareness of the potential safety concerns with the use of sodium phosphate/sodium biphosphate enemas, the Pharmacy Benefits Management Services (PBM), Medical Advisory Panel (MAP) and VISN Pharmacist Executives (VPEs) developed the “Sodium Phosphate/Sodium Biphosphate, Enema: Safety Considerations” (see [Sodium Phosphate Sodium Biphosphate Enema, Safety Considerations](#)). The information includes conditions where sodium phosphate/sodium biphosphate enemas are contraindicated, as well as where they

- With impaired renal function (eGFR 30 to 60 ml/min) or other comorbidities, such as gastrointestinal (including dysmotility, colonostomy), hepatic (including ascites), neurologic, cancer, pulmonary or cardiovascular disorders
- Taking medications known to affect renal perfusion or function, or hydration status
- With pre-existing electrolyte disturbances or who are taking diuretics or other medication which may affect electrolyte levels
- Who are taking medications known to prolong the QT interval
- More than 64 years of age or less than 6 years old
- Who are pregnant or nursing a baby
- Patients with conditions that may predispose to dehydration or those taking medications that may decrease glomerular filtration rate, such as diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARBs), or nonsteroidal anti-inflammatory drugs (NSAIDs), should be assessed for hydration status prior to use and managed appropriately

PRECAUTIONS

In order to assist with implementation of the safe use of sodium phosphate/sodium biphosphate enemas, the following measures will be undertaken:

- The VPEs will discuss the Sodium Phosphate/Sodium Biphosphate Enema Safety Considerations at the VISN/local level so that leadership at all VAMCs are alerted to the concerns in patients with chronic kidney disease as well as other safety considerations (including contraindications, warnings/precautions, and recommended dosing of sodium phosphate/sodium biphosphate enemas, especially for patients with constipation) and can implement methods to alert providers as deemed appropriate by the VISN/facilities.
- At the VISN/local level, leadership should engage local gastroenterologists (and other experts) to review the appropriate use of sodium phosphate/sodium biphosphate enemas for adequate, yet safe bowel cleansing prior to a procedure.

In an effort to evaluate whether sodium phosphate/sodium biphosphate enema is being used inappropriately on a chronic basis for constipation, the VA Center for Medication Safety will review outpatient utilization via a Medication Use Evaluation (MUE).

Contributed by: Elaine Furmaga, Pharm.D.
and Francine Goodman, Pharm.D., BCPS

Helping to achieve safe medication use

IMPORTANT CHANGE WITH HEPARIN LABELS

(continued from page 1)

- administration of heparin.
- Engage patient safety providers and nursing in educational efforts. Consider including information in newsletters, e-mail announcements, computer screen banners, and other forms of communication your medical center may use (such as daily bulletins).
- Engage informatics staff to review quick orders, drug menus, etc., to ensure language is consistent with new labels.
- Consider independent double checks during the dispensing and administration phases.
- Widely share the April 2013 Issue of Medication Safety in Seconds ([Issue 4; Volume 3; April 2013](#)), a safety newsletter

published by the VA Center for Medication Safety (VA MedSAFE) in conjunction with the National Pharmacy Benefits Management Services (PBM) which highlights this change.

Additional information can be found at:

- <http://www.ajhp.org/content/70/8/650.2.full?etoc>
- <http://www.usp.org/usp-healthcare-professionals/medication-safety-labeling/heparin-labeling-changes>

REFERENCES:

NAN ALERT. Important change with heparin labels. National Coordinating Council on Medication Error Reporting and Prevention (NCCMERP): June 10, 2013.

(continued from page 2)

from the fda

- Advise that ketoconazole oral tablets can lead to harmful drug interactions with other medications** [*Precautions* section].
 - Ketoconazole is one of the most potent inhibitors of the cytochrome P450 3A4 isoenzyme (CYP3A4). The clearance of other co-administered drugs that are metabolized by CYP3A4 is decreased by ketoconazole and can result in increased drug concentrations in plasma, which can predispose patients to potentially serious adverse reactions including QT prolongation.

CARDIOLOGY

[FDA approves label changes to include intestinal problems \(sprue-like enteropathy\) linked to blood pressure medicine olmesartan medoxomil](#)

7/3/2013

FDA has approved changes to the labels of olmesartan medoxomil products (Benicar, Benicar HCT, Azor, Tribenzor, and generics) to include the risk of sprue-like enteropathy associated with use of these drugs. Twenty-three cases identified from FDA's Adverse Event Reporting System (FAERS) as well as 22 cases described in the literature document severe diarrhea and weight loss resolving upon discontinuation. Symptoms of severe, chronic diarrhea with substantial weight loss may develop months to years after initiation of olmesartan therapy. If no other etiology exists for the intestinal symptoms, olmesartan should be discontinued and replaced with another antihypertensive treatment.

VA addressed the issue of olmesartan and case reports of sprue-like enteropathy in last month's issue ([Issue 6; Volume 3; June 2013](#)).

MENTAL HEALTH

[FDA is investigating two deaths following injection of long-acting antipsychotic Zyprexa Relprevv \(olanzapine pamoate\)](#)

6/18/2013

Two unexplained deaths occurred 3-4 days after intramuscular (IM) injection of the antipsychotic drug olanzapine pamoate (Zyprexa Relprevv). High doses of olanzapine pamoate (Zyprexa Relprevv) can result in delirium, cardiopulmonary arrest, cardiac arrhythmias, and reduced level of consciousness (ranging from sedation to coma). Clinical trials supporting approval of olanzapine pamoate (Zyprexa Relprevv) have documented cases of post-injection delirium sedation syndrome (PDSS), where the drug rapidly enters the blood stream after an injection causing elevated blood levels, delirium, and sedation. However, these symptoms took place within 3 hours after administration and no deaths ensued. FDA recommends that health care providers continue to follow drug label recommendations and Risk Evaluation and Mitigation Strategy (REMS) requirements including:

- 1) administering olanzapine pamoate (Zyprexa Relprevv) injection to patients at a REMS-certified facility;
- 2) continuously monitoring at the REMS-certified facility for at least 3 hours following an injection; and
- 3) ensuring accompaniment home from the facility.

NEWSWORTHY...