

MEDICATION

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

SAFETY IN SECONDS

IN THIS ISSUE:

- ▶ INRatio AND INRatio2 PT/INR MONITOR SYSTEM BY ALERE: RECALL DUE TO POTENTIALLY INACCURATE INR RESULTS..... 1
- ▶ MEDICATION SAFETY NEWS FROM THE VA NATIONAL PHARMACY BENEFITS MANAGEMENT SERVICES [PBM] AND THE FOOD AND DRUG ADMINISTRATION [FDA] 1-4
- ▶ ATTENTION PHARMACISTS!!! OPPORTUNITIES TO PARTICIPATE IN NATIONAL QUALITY IMPROVEMENT INITIATIVES.....4

**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.

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Helping to achieve safe medication use

INRatio AND INRatio2 PT/INR MONITOR SYSTEM BY ALERE: RECALL DUE TO POTENTIALLY INACCURATE INR RESULTS

In December 2014, Alere initiated a voluntary correction to inform users of the INRatio and INRatio2 PT/INR Monitoring System that patients with certain medical conditions should not be tested with the system due to the potential for inaccurate results. Details were addressed in a previous issue of this newsletter ([Issue 1; Volume 5; January 2015](#)). Since that time, the manufacturer has built software enhancements to address the errors within these monitoring systems and submitted these developments to the FDA.

However, FDA notified the company that the company's data do not adequately show effectiveness of the software modification. FDA recommends that Alere take steps to voluntarily remove the INRatio device from the market, including:

- Ensure an orderly transition for patients requiring anticoagulation monitoring;
- Provide a timeline to discontinue product line;
- Offer information on patient transition to patients and healthcare providers.

NEWSWORTHY...

from the pbm

- Lithium Safety – 07/25/16 – [National PBM Bulletin](#)
- Various Diabetic Test Strips Recall (specific sites only) – 07/12/16 – [National PBM Patient Level Recall Communication](#)
- Contaminated Oral Liquid Docusate – 06/29/16 - [National PBM Patient Level Recall Communication](#)
- Fluoroquinolone Safety – 06/03/16 - [National PBM Bulletin](#)

(continued on page 2)

from the fda

(continued from page 1)

INFECTIOUS DISEASE

[FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects](#)

7/26/2016

FDA revised the *Boxed Warning* of fluoroquinolone products and also added a new warning based on the results of its safety review last May that showed that systemic use (i.e. tablets, capsules, and injectables) of fluoroquinolones is associated with disabling and potentially permanent serious side effects involving the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient. The labels of fluoroquinolone medicines already have a *Boxed Warning* for tendinitis, tendon rupture, and worsening of myasthenia gravis. The labels also include warnings about the risks of peripheral neuropathy and central nervous system effects as well as other serious risks such as cardiac, dermatologic, and hypersensitivity reactions associated with fluoroquinolones. In addition to updating information in the *Boxed Warning*, the *Indications and Usage* section contains new language reserving the use of fluoroquinolones for patients who do not have other available treatment options for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI). For further details, please see last month's issue ([Issue 6: Volume 6: June 2016](#)) as well the [National PBM Bulletin](#) released in June.

ENDOCRINOLOGY

[FDA strengthens kidney warnings for diabetes medicines canagliflozin \(Invokana, Invokamet\) and dapagliflozin \(Farxiga, Xigduo XR\)](#)

6/14/2016

FDA has strengthened the existing warning about the risk of acute kidney injury for the type 2 diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR); however, FDA does not mention whether empagliflozin (Jardiance) carries the same risk. This is based on 101 cases of acute kidney injury reported to FDA's Adverse Event Reporting System (FAERS) from March 2013 to October 2015 that demonstrate a temporal relationship with canagliflozin (73 patients) and dapagliflozin (28 patients). Of these 101 cases:

- 96 resulted in hospitalization for evaluation and management of acute kidney injury;
- 22 cases involved admission to an intensive care unit;
- 4 deaths occurred during hospitalization, 2 of which were cardiac-related.
- 15 patients received dialysis:
 - ◊ 3 patients had a history of chronic kidney disease or previous acute kidney injury; and
 - ◊ 6 reported concomitant use of both an angiotensin-converting enzyme (ACE) inhibitor and a diuretic.
- In 58 cases, the time to onset of acute kidney injury occurred within one month or less of initiating the drug.
- 78 cases reported drug discontinuation:
 - ◊ 56 cases reported improvement;
 - ◊ 11 patients did not recover, which included the 4 deaths noted previously;
 - ◊ 3 patients recovered with sequelae upon discontinuation.

FDA recommends that:

- Before initiating canagliflozin or dapagliflozin, consider factors that may predispose patients to acute kidney injury, including hypovolemia, chronic renal insufficiency, congestive heart failure, and concomitant medications such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs).
- Evaluate renal function prior to initiating canagliflozin or dapagliflozin and monitor periodically thereafter.
- Consider temporarily discontinuing canagliflozin or dapagliflozin in any setting of reduced oral intake such as acute illness or fasting, or with fluid losses such as gastrointestinal illness or excessive heat exposure.
- Monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue canagliflozin or dapagliflozin promptly and institute treatment.

(continued on page 3)

from the fda

(continued from page 2)

- Instruct patients to seek medical attention immediately if they experience signs and symptoms while taking these medicines such as:
 - ◊ Decreased urine
 - ◊ Swelling in legs or feet
- Inform patients to not stop or change their diabetes medicines without first talking to their health care professional as uncontrolled blood sugar levels may ensue.

GASTROENTEROLOGY

[FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide \(Imodium\), including from abuse and misuse](#)

6/7/2016

Higher than recommended doses of loperamide can cause serious cardiac events, including QT interval prolongation, Torsades de Pointes, other ventricular arrhythmias, cardiac arrest, syncope, and death. In the majority of severe cases, individuals intentionally abused loperamide by taking massive doses to achieve a feeling of euphoria or prevent opioid withdrawal. Some patients also misused loperamide by taking higher than recommended doses to treat diarrhea. In several cases, individuals used concomitant drugs to increase gastrointestinal absorption, decrease loperamide metabolism, and increase blood brain barrier penetration. These drugs included CYP3A4 inhibitors (e.g., itraconazole, clarithromycin), CYP2C8 inhibitors (e.g., gemfibrozil), and P-glycoprotein inhibitors (e.g., quinidine).

FDA recommends that providers:

- Prescribe loperamide with caution in patients at risk for QT interval prolongation, Torsades de Pointes, and other serious arrhythmias or who utilize drugs that inhibit loperamide metabolism or transport (i.e., CYP3A4, CYP2C8, or P-glycoprotein inhibitors). Concomitant drugs may act synergistically to increase loperamide concentrations by blocking more than one pathway of loperamide elimination.
- Counsel patients about the cardiac risks of loperamide and tell them not to use more than the recommended dose.
- If loperamide-induced cardiotoxicity is suspected:
 - ◊ Discontinue loperamide and start therapy to manage and prevent cardiac arrhythmias and severe outcomes.
 - ◊ Measure blood levels of loperamide, which may require specific testing.
 - ◊ Consider electrical pacing or cardioversion for loperamide-associated Torsades de Pointes that persists despite pharmacotherapy.

[FDA warns about serious bleeding risk with over-the-counter antacid products containing aspirin](#)

6/6/2016

Over-the-counter (OTC) aspirin-containing antacid products used to treat heartburn, sour stomach, acid indigestion, or upset stomach have existing warnings on their labels about bleeding risk; however, FDA continues to receive reports of this serious safety issue. Out of 41 cases identified by the FDA Adverse Event Reporting System (FAERS) from 1969-2014, all experienced serious outcomes resulting in hospitalization, and 21 patients required transfusions due to the blood loss. Most of the patients recovered; one death was reported. Risk factors for developing bleeding were reported in 88% (36/41) of the cases, and included age greater than 60 years (n=23); use of anticoagulants, steroids, or nonsteroidal anti-inflammatory drugs (n=28); history of stomach ulcers (n=4); or history of alcohol abuse (n=5). FDA continues to evaluate this safety concern and plans to convene an advisory committee of external experts to provide input regarding the need for additional actions.

CENTRAL NERVOUS SYSTEM

[FDA evaluating the risk of burns and scars with Zecuity \(sumatriptan\) migraine patch](#)

6/2/2016

Since marketing began in September 2015, the sumatriptan (Zecuity) patch, used to treat acute migraine

(continued on page 4)

from the fda

(continued from page 3)

headaches in adults, has been associated with a large number of reports of burning or scarring on the skin where the patch was worn. Descriptions include severe redness, pain, skin discoloration, blistering, and cracked skin. As such, the manufacturer has decided to temporarily suspend sales, marketing, and distribution to investigate the cause of burns and scars associated with the Zecuity patch. Health care professionals should discontinue prescribing Zecuity, and patients should stop using any remaining patches and contact their prescribers for an alternative migraine medicine.

Getting the most from our safety surveillance

ATTENTION PHARMACISTS!!! OPPORTUNITIES TO PARTICIPATE IN NATIONAL QUALITY IMPROVEMENT INITIATIVES

- VAMedSAFE is collaborating with the Antimicrobial Stewardship Task Force (ASTF) on a third medication use evaluation (MUE). The title of this MUE is “Evaluation of the Management of Acute Respiratory Tract Infections for Veterans in the Outpatient Setting.” The overarching goal is to determine if the documentation of diagnostic criteria and treatment of Acute Respiratory Tract Infections (ARI)s in Veterans are consistent with the evidence-based Centers for Disease Control and Prevention (CDC) Get Smart ARI treatment recommendations. We hope to have 25 VAMCs participate in the MUE. If interested, please email Muriel.Burk@va.gov by August 31, 2016. (Submitted by Muriel Burk, Pharm.D.)
- PBM VAMedSAFE has made available the MUE toolkit for the second centrally aggregated MUE (CAMUE 2) focusing on digoxin use in A-fib and has 14 sites participating already.

CAMUE is one of the national MUE programs that provides the local VAMC with the tools necessary to conduct and analyze the entire MUE at the site level, with PBM only receiving aggregate facility-level summary reports. This might be a good opportunity for residents, although others are also encouraged to participate. Information on CAMUE 2 and the Excel registration form can be found on the Sharepoint site:

<https://vaww.cmopnational.va.gov/CR/VAMedSAFEMultiSiteResearch/camue/default.aspx>

Completed forms should be sent to:
Madeline.McCarren@va.gov.

The deadline for registration has been extended to September 30, 2016. Data are due at VAMedSAFE 3 months after registration. (Submitted by Madeline McCarren, Ph.D., MPH) ■