

MEDICATION

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

SAFETY IN SECONDS

Helping to achieve safe medication use

FORMULARY IMPLICATIONS OF KETOCONAZOLE SAFETY ISSUES

In July 2013, FDA limited usage of ketoconazole oral tablets due to:

- Potentially fatal liver injury;
- Risk of drug interactions that may lead to QT prolongation; and
- Adrenal gland problems.

Complete details regarding these safety issues can be found in the FDA's Drug Safety Communication (<http://www.fda.gov/Drugs/DrugSafety/ucm362415.htm>) as well as the last issue of *Medication Safety in Seconds* (Issue 7; Volume 3; July/August 2013). As such, ketoconazole oral tablets are now FDA-indicated only for the treatment of blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis in patients with suboptimal response and/or intolerance to other treatments. The use of ketoconazole tablets in *Candida* and dermatophyte infections is no longer indicated. Ketoconazole should only be used when other effective antifungal ther-

apy is not available or tolerated and the potential benefits outweigh the potential risks.

Although not FDA-approved, ketoconazole is prescribed (off-label) as an alternative agent for prostate cancer and is rarely used off-label in Cushing's syndrome. Consequently, ketoconazole will now be listed on the VA National Formulary (VANF) with a restriction to hematology-oncology, as opposed to the former anti-infective restrictions. As a result, non-formulary review will need to occur for uses in infectious diseases, dermatology, endocrine, etc.

REFERENCES:

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. <http://www.fda.gov/Drugs/DrugSafety/ucm362415.htm>. Accessed 09/24/2013.

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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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NEWSWORTHY...

from the pbm

- Nova Max Glucose Test Strips Recall Due To Falsely Elevated Blood Glucose Results – 08/14/13 – [National PBM Communication](#)
- Valproate Use During Pregnancy and Lower IQ in Children Exposed – 08/06/13 – [National PBM Bulletin](#)

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from the fda

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NEUROLOGY

[FDA Drug Safety Communication: FDA investigating rare brain infection in patient taking Gilenya \(fingolimod\)](#)

8/29/2013

FDA reports the first case of progressive multifocal leukoencephalopathy (PML) following the administration of Gilenya in a patient in Europe. The patient, with multiple sclerosis (MS), had not previously received Tysabri (natalizumab), an MS drug associated with a higher risk of PML. The patient received approximately eight months of Gilenya treatment prior to the PML diagnosis. Before initiating Gilenya treatment the patient received interferon beta-1a and azathioprine for approximately one month (both were discontinued when Gilenya was started) as well as multiple courses of intravenous corticosteroids for several months before and during Gilenya treatment. PML diagnosis ensued from clinical symptoms and the detection of JC viral DNA in the cerebrospinal fluid. Gilenya treatment was stopped. FDA continues to investigate the details of this case in collaboration with the manufacturer. In the meantime, FDA recommends that patients should not stop taking Gilenya without first discussing any questions or concerns with their health care professionals.

INFECTIOUS DISEASES

[FDA requires label changes to warn of risk for possibly permanent nerve damage from antibacterial fluoroquinolone drugs taken by mouth or by injection](#)

8/15/2013

Although risk of peripheral neuropathy has been documented in product information of systemic fluoroquinolone drugs since 2004, FDA has required manufacturers to make revisions to the drug labels (*Warnings/Precautions* and *Warnings and Precautions* sections) as well as the Medication Guides to better:

- Characterize the risk of peripheral neuropathy associated with the class of systemic fluoroquinolones; and
- Describe the potential rapid onset in addition to the risk of permanence.

FDA's recent review of the Adverse Event Reporting System (AERS) showed a continued association between fluoroquinolone use and disabling peripheral neuropathy, with rapid onset (within a few days of treatment) and symptoms persisting for more than a year despite discontinuation of the fluoroquinolone in some patients. FDA has not identified any specific risk factors for the development of peripheral neuropathy, such as duration of therapy or age of the patient. FDA recommends that if a patient develops symptoms of peripheral neuropathy while using a systemic fluoroquinolone, the fluoroquinolone should be stopped, and the patient should be treated with an alternative non-fluoroquinolone antibacterial drug, unless the benefit of continued treatment with a fluoroquinolone outweighs the risk. Approved fluoroquinolone drugs include levofloxacin (Levaquin), ciprofloxacin (Cipro), moxifloxacin (Avelox), norfloxacin (Noroxin), ofloxacin (Floxin), and gemifloxacin (Factive). Topical fluoroquinolone formulations (applied to the ears or eyes) are not known to cause this risk.

PAIN MANAGEMENT

[FDA Drug Safety Communication: FDA warns of rare but serious skin reactions with the pain reliever/fever reducer acetaminophen](#)

8/1/2013

FDA requires additional warning in the labels of prescription and over-the-counter (OTC) drug products containing acetaminophen to address evidence found in FDA's Adverse Event Reporting System (FAERS) database and the medical literature of the risk of rare, but fatal serious skin reactions [Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP)].

- 3 published cases link acetaminophen with serious skin reactions due to recurrence of symptoms on rechallenge.
- 3, 17, and 6 cases of SJS, TEN, and AGEP (respectively) demonstrated hypersensitivity to acetaminophen only; cases resulted in hospitalizations, but not deaths, and all resolved upon discontinuation of acetaminophen.
- 5 SJS/TEN case-control studies and 1 of AGEP indicated an increased risk of SJS/TEN with the use of acetaminophen, independent of the effects of other drugs.
- From 1969 to 2012, FAERS identified 91 cases of SJS/TEN and 16 cases of AGEP involving single-ingredient acetaminophen products, which resulted in 67 hospitalizations and 12 deaths.

FDA recommends provider and patient awareness of this rare risk and to consider acetaminophen, along with other drugs already known to have such an association, when assessing patients with potentially drug-induced skin reactions. Symptoms include reddening of the skin, rash, blisters, and detachment of the upper surface of the skin. No cross-sensitivity exists between acetaminophen and other pain reliever/fever reducer drugs.

Getting the most from our safety surveillance

VASOPRESSIN AND HYDRALAZINE POTENTIAL LOOK-ALIKE CONFUSION

In one local facility, look-alike confusion occurred between a vial of vasopressin and a vial of hydralazine due to the nearly identical appearance in blue and white packaging between a new lot of vasopressin vials and hydralazine vials (see Figure 1), as opposed to the usual orange-colored vasopressin packaging. In this instance, a vasopressin vial was found in the hydralazine slot in the anesthesia cart of the anesthesia medication room. Further inspection of additional anesthesia carts uncovered more vials of vasopressin in 5 other carts. The site did not report any actual errors in administration of these agents to patients or any adverse outcomes related to this look-alike confusion.¹

Vasopressin and hydralazine exert opposite effects on peripheral vasculature and blood pressure. Vasopressin is a vasoconstricting agent that increases peripheral vascular resistance, thereby increasing arterial blood pressure. It also acts to maintain the body's homeostasis by regulating water, glucose, and salts in the blood. On the other hand, hydralazine is a vasodilating agent that decreases peripheral resistance to lower blood pressure.^{2,3} Patients who inadvertently receive vasopressin in place of the intended hydralazine may experience an opposite hypertensive result instead of the expected hypotensive effect. Conversely, if a patient mistakenly receives hydralazine instead of the intended vasopressin in acute situations such as hypovolemic shock which may occur during hemorrhage, there will be no compensatory mechanism for restoring blood pressure. In addition, if not managed properly, the patient may experience undesirable side-effects of hydralazine from sympathetic stimulation (i.e., increased heart rate and cardiac output), which may lead to angina pectoris or myocardial infarction in at-risk patients.

When medications have look-alike packaging as in this case, an ever-present danger looms that the wrong medication may be transported and/or stocked in areas of use. Sometimes vials' cap covers can be misleading, especially if one cap color has been

consistently associated with a particular drug, and the product is stored only with the caps in view. The medical center took the following steps as corrective action to limit the potential for error:

- *Effective immediately all vasopressin vials have been removed from the anesthesia medication room and will no longer be stocked.*
- *Pharmacy will provide a limited number of infusions and pre-prepared syringes of vasopressin. The only cases where vasopressin would routinely be used would be liver transplant and cases where the aorta is going to be cross-clamped.*
- *In emergency situations, vasopressin is stocked in the master crash carts. A supply of vasopressin is available for use as these changes are put into effect.*

The VA National Center for Patient Safety (NCPS) has suggested additional measures as strong actions to help minimize look-alike/sound-alike confusion, such as:

- Using various drug delivery systems to help differentiate products, such as amps, vials, and syringes;
- Using different manufacturers or package sizes to distinguish between products;
- Using lidded storage bins and bar coding to assure the correct agent when adding or replenishing the dispensing unit.⁴

Refer to the side bar for other error-prevention strategies recommended by the VA Pharmacy Benefits Management Services (PBM) and Center for Medication Safety (MedSAFE).

REFERENCES:

1. Internal data.
2. PITRESSIN® (vasopressin injection, USP) [prescribing information]. Rochester, MI: JHP Pharmaceuticals, LLC; January 2010.
3. Hydralazine Hydrochloride Injection, USP [prescribing information]. Schaumburg, IL: APP Pharmaceuticals, LLC; January 2008.
4. Trettin, KW. Look-Alike/Sound-Alike Medications – What Can Be Done? *Topics in Patient Safety (TiPS)* 2007; 7(2): 1,4.



Figure 1. Vials of vasopressin and hydralazine were mixed up.

PROVIDER RECOMMENDATIONS

- **Providers should be aware of the potential for look-alike confusion between 20 units/mL vasopressin injection, USP (1 mL vial) and 20mg/mL hydralazine hydrochloride injection, USP (1mL single dose vial) due to similar packaging and label color.**
- **Providers should carefully check the name on the vial when either 20 units/mL vasopressin injection, USP (1 mL vial) or 20mg/mL hydralazine hydrochloride injection, USP (1mL single dose vial) is ordered and/or administered.**
- **Pharmacy should ensure that a process is in place to return unused stock of 20 units/mL vasopressin injection, USP (1 mL vial) and 20mg/mL hydralazine hydrochloride injection, USP (1mL single dose vial) to designated pharmacy or operating room area(s) when not ordered for a particular patient.**
- **Pharmacy should review their stock for 20 units/mL vasopressin injection, USP (1 mL vial) and 20mg/mL hydralazine hydrochloride injection, USP (1mL single dose vial), and ensure that a method is in place to distinguish between the two agents in order to avoid future look-alike confusion (i.e., warning stickers/labels).**
- **Pharmacy should ensure that a system is in place to notify providers regarding the use of new manufacturers and/or new product appearance/package to reduce the potential for medication error, especially for critical drug products used in acute or emergency care.** ■