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MEDICATION SAFETY IN SECONDS

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

Helping to achieve safe medication use

AFLIBERCEPT (EYLEA) INJECTION AND RISK OF INTRAOCULAR INFLAMMATION (IOI) WITH SYRINGES PACKAGED IN CERTAIN LOTS OF KIT

Reports of intraocular inflammation (IOI) associated with use of aflibercept (Eylea) injections have increased after administration of specific lots, according to the manufacturer. Aflibercept (Eylea) is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD); macular edema following retinal vein occlusion (RVO); diabetic macular edema (DME); and diabetic retinopathy (DR) in patients with DME. Aflibercept (Eylea) is supplied as a carton containing one single-use, sterile, 3-mL, glass vial designed to deliver 0.05mL of 40mg/mL of aflibercept (Eyelea); one 19-gauge x 1 ½-inch, 5-micron, filter needle for withdrawal of the vial contents; one 30-gauge x 1/2-inch injection needle for intravitreal injection; and one 1-mL syringe for administration.

Product labeling lists IOI as one of the most common adverse reactions (≥1%) observed in clinical trials. Based on post-marketing surveillance, 1 to 4 cases of IOI is reported per 10,000 injections annually. A retrospective analysis of post-marketing reports of aflibercept-related sterile inflammation voluntarily reported by 12 practices throughout the United States to the American Society of Retina Specialists (ASRS) Therapeutic Surveillance Committee (TSC) from December 1, 2011, through February 12, 2014, suggests that among 56 reported cases of sterile inflammation, mean time to onset was 3.5 days; most cases consisted of initial loss of vision and severe pain; 37 cases (66%) were treated with topical corticosteroids and/or observation alone with a mean time to resolution of 28.6 days (median, 28 days; range, 4-84 days). However, some patients developed permanent vision loss.

With the rise of recent reports of IOI, the manufacturer conducted a review of their manufacturing processes as well as external components included for administration in the final packaged kit (i.e., non-drug supplies like syringes and needles). Findings suggested that certain batches of syringes included in particular lots of aflibercept (Eylea) were

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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.

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

NEWSWORTHY...

from the pbm

- Sofosbuvir/Velpatasvir (Epclusa) and Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi) Look-Alike/Sound-Alike Potential – 01/26/2018 - National PBM Bulletin

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from the fda

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NEUROLOGY

FDA working with manufacturers to withdraw Zinbryta from the market in the United States

3/2/2018

Cases of serious inflammatory brain disorders, including immune-mediated encephalitis and meningoencephalitis, have been reported in patients treated with daclizumab (Zinbryta), an interleukin-2 receptor blocking antibody indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS). The European Medicines Agency (EMA) has recommended a recall and, in parallel, the manufacturer has decided to voluntarily withdraw daclizumab (Zinbryta) from the global market on March, 2, 2018. FDA is working closely with the manufacturers to help ensure a well-organized withdrawal from the market in the United States. The drug will be available for patients as needed until April 30, 2018. No new patients will start taking daclizumab (Zinbryta) or participate in clinical studies. Patients using daclizumab (Zinbryta) should not stop their medication without talking with their doctor and should contact their doctor immediately if they have any new and unexplained symptoms. According to product labeling, patients discontinuing the product should have serum transaminase levels and total bilirubin levels monitored monthly for 6 months after receiving their last dose, given the potential for liver injury. Healthcare professionals should inform impacted patients that adverse drug reactions may occur up to 5 months after discontinuation and to contact their provider immediately if they develop clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine).

HEPATIC IMPAIRMENT

FDA adds Boxed Warning to highlight correct dosing of Ocaliva (obeticholic acid) for patients with a rare chronic liver disease

2/1/2018

FDA continues to receive reports that obeticholic acid (Ocaliva) is being incorrectly dosed daily instead of weekly in primary biliary cholangitis (PBC) patients with moderate to severe liver impairment. Higher doses than recommended in the drug label can increase the risk for liver decompensation, liver failure, and sometimes death. FDA has added a Boxed Warning to the drug label and requires a Medication Guide for patients to discuss this risk.

FDA recommends that healthcare professionals:

- Routinely monitor all patients for biochemical response, tolerability, and PBC progression, and re-evaluate Child-Pugh classification to determine if dosage adjustment is needed.
- Closely monitor patients at risk of liver decompensation, including those with laboratory evidence of worsening liver function (e.g., total bilirubin, INR, albumin) or progression to cirrhosis.
- Educate patients and caregivers on the symptoms of worsening liver function .

Any of the following specific symptoms	Any of the following general symptoms if they are severe or do not go away
• Abdominal swelling • Yellow eyes or skin • Bloody or black stools • Coughing up or vomiting blood • Mental changes such as confusion, more sleepy than usual or harder to wake up, slurred speech, mood swings, or changes in personality	• Stomach area pain • Nausea, vomiting, or diarrhea • Loss of appetite or weight loss • New or worsening tiredness • Weakness • Fever and chills • Lightheadedness • Less frequent urination

- Temporarily stop obeticholic acid (Ocaliva) in patients with laboratory or clinical evidence of worsening liver function that may indicate decompensation and monitor the patient's liver function. If a patient's condition returns to baseline, weigh the potential risks and benefits of restarting obeticholic acid (Ocaliva) . Re-initiate, using the recommended starting dosage based on Child-Pugh classification.
- Consider discontinuation in those who have experienced clinically significant liver-related adverse reactions.

Getting the most from our safety surveillance

HYDROCHLOROTHIAZIDE AND POTENTIAL ASSOCIATION WITH NON-MELANOMA SKIN CANCER

Submitted by: Elaine Furmaga, Pharm.D.

Summary
Hydrochlorothiazide, a thiazide diuretic, is widely used in VA for hypertension. Due to its demonstrated benefit in reducing cardiovascular events and cardiovascular and total mortality, the VA/DoD hypertension treatment guidelines give a strong recommendation for using thiazide-type diuretics as first-line therapy for hypertension. Recently, a case-control study reported that use of hydrochlorothiazide was associated with an increased risk of non-melanoma skin cancer. This information is being provided to assist clinicians in determining the risk versus benefit of treatment based on the available data and quality of the evidence. In addition, as hydrochlorothiazide is one of many medications that can be photosensitizing, it is important for providers to be aware of this potential association when examining patients, and to educate patients on methods to minimize adverse effects of sun exposure.

Medications and Photosensitivity
Certain medications are considered photosensitizing, causing a phototoxic reaction (increasing sensitivity of the skin to sun exposure), resulting in severe sunburn; or a photoallergic reaction (immunogenic response), presenting with urticaria and erythema.

Examples of medications that may cause photosensitivity include: amiodarone; antibiotics (e.g., ciprofloxacin, tetracycline, trimethoprim); antifungals; antihistamines; statins; diuretics (e.g., thiazides, furosemide, triamterene); non-steroidal anti-inflammatory drugs; oral contraceptives and estrogens; phenothiazines; psoralens; retinoids; sulfonamides; and sulfonylureas. Hydrochlorothiazide (a thiazide diuretic), as well as chlorthalidone and indapamide (described as thiazide-like diuretics) report photosensitivity as a potential adverse reaction in their respective drug labeling.

Summary of Recent Data
Previously, a case control study (Robinson et al., 2013) suggested an increased risk of squamous cell carcinoma (SCC) (OR 1.2 95% CI 1.0 to 1.4) or basal cell carcinoma (BCC) (OR 1.2 95% CI 0.9 to 1.5) with photosensitizing medications. The risk for SCC was also reported to be numerically increased for diuretics (OR 1.3 95% CI 0.9 to 2.0), and for thiazide diuretics (OR 1.3 95% CI 0.7 to 2.4), although the results were not statistically significant. The authors noted that for SCC, the association was strongest in patients with a tendency to sunburn rather than tan.

More recently, another case control study (Pederson et al., 2017) specifically evaluating use of hydrochlorothiazide, reported a significant association for both SCC (adjusted OR 1.75 95% CI 1.66 to 1.85) and BCC (adjusted OR 1.08 95% CI 1.05 to 1.10). Results were adjusted for some medications known to cause photosensitivity. Limitations included the lack of information on UV exposure or skin phenotype (noted as two major risk factors for SCC and BCC). The investigators observed that the population studied (Danish) would not be expected to differ in sun habits or skin type depending on use or nonuse of hydrochlorothiazide. The authors also reported that per the subgroup analysis, there was a stronger association among younger individuals and females. In addition, there was an increased risk associated with high use (cumulative amount) of hydrochlorothiazide.

Given the limitations of these case control studies, additional data are needed to confirm an association with hydrochlorothiazide (and/or other photosensitizing medications) with non-melanoma skin cancer. Use of a thiazide-type diuretic remains a primary treatment for hypertension given the evidence for cardiovascular and mortality benefit. However, it is still prudent to promote awareness of the risk for an adverse event with photosensitizing medications, and to review the importance of adequate sun protection with patients.

Patient Education
In general, patients should be informed of ways to minimize risk of skin damage from sun or exposure to UV rays; with special emphasis in patients taking medications that may be photosensitizing. Such counseling includes to:

- Limit exposure to direct sunlight
- Use sunscreen (follow the label directions for proper application)
- Protect skin with clothing
- Wear a hat with adequate coverage
- Wear sunglasses that block UV rays
- Avoid use of tanning beds or sun lamps

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Helping to achieve safe medication use

AFLIBERCEPT (EYLEA) INJECTION AND RISK OF INTRAOCULAR INFLAMMATION (IOI) WITH SYRINGES PACKAGED IN CERTAIN LOTS OF KIT

(continued from page 1)

Table 1. Lot numbers of affected product.

8148200076	8148200092	8148200094	8148200104
8148200090	8148200093	8148200095	8148200105

linked to the development of IOI. The manufacturer did not identify any association of increased reporting of IOI with the drug itself.

Lot numbers of aflibercept (Eylea) kits with affected syringes are listed in Table 1.

Although the manufacturer is not issuing a formal recall, they distributed a letter to healthcare providers last month stating the following voluntary actions/recommendations:

- Aflibercept (Eylea) kits with affected syringes will no longer be distributed.
- Practitioners should not use the syringes provided in the affected aflibercept (Eylea) kits.
- Affected aflibercept (Eylea) kits may be exchanged for kits with different syringes by contacting the manufacturer.
- The manufacturer contacted the U.S. Food and Drug Administration (FDA) and the American Society of Retina Specialists (ASRS) with their findings and action plan.
- The manufacturer plans to report their findings in greater detail as they continue to investigate.

Within the VA healthcare system, a VA Internal Recall was issued to remove affected product from use and inventory. The current recall is posted as PRO-12804 [Internal VA Recall of Certain Lots of Eylea] on the National Center for Patient Safety Product Recall Office website (available on the VA intranet at http://vaww.recalls.ncps.med.va.gov/WebRecalls/Recalls.html). Providers should continue to report any adverse reactions with the use of aflibercept (Eylea) by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA- 1088, fax 1-800- FDA-0178, online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm , or by mail).

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