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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

HERCEPTIN® [TRASTUZUMAB] AND KADCYLA™ [ADO-TRASTUZUMAB EMTANSINE]: POTENTIAL LOOK-ALIKE/SOUND-ALIKE NAME PAIR CONFUSION

Potential look-alike/sound-alike confusion may occur with HERCEPTIN® [trastuzumab] and KADCYLA™ [ado-trastuzumab emtansine] due to similar generic names and indications for breast cancer. Some written and online publications as well as health information systems are incorrectly referring to KADCYLA™ [ado-trastuzumab emtansine] as "trastuzumab emtansine" without using the "ado" prefix and hyphen, which may lend to mix-ups with HERCEPTIN® [trastuzumab] and potential medication errors. According to the FDA, such errors occurred during the clinical trials involving KADCYLA™ [ado-trastuzumab emtansine], where four patients received KADCYLA™ [ado-trastuzumab emtansine] 6 mg/kg instead of the intended drug HERCEPTIN® [trastuzumab] 6 mg/kg. No adverse event information was available.

KADCYLA™ [ado-trastuzumab emtansine] , as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

- Received prior therapy for metastatic disease, or
- Developed disease recurrence during or within six months of completing adjuvant therapy.

According to the product labeling, the recommended dose of KADCYLA™ [ado-trastuzumab emtansine] is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. *Do not administer KADCYLA™ [ado-trastuzumab emtansine] at doses greater than 3.6 mg/kg. Do not substitute KADCYLA™ [ado-trastuzumab emtansine] for or with HERCEPTIN® [trastuzumab].* Safety concerns associated with KADCYLA™ [ado-trastuzumab emtansine] include a boxed warning for

(continued on page 3)

NEWS YOU CAN USE

FROM THE VA NATIONAL PBM: BULLETINS, COMMUNICATIONS, & RECALLS

Genentech Dear Pharmacist Letter: Cathflo® Activase® (alteplase) and Particulate Matter

Genentech issued a Dear Pharmacist Letter dated March 22, 2013 stating that some vials of Cathflo® Activase® (alteplase) contain rubber stopper particulates after reconstitution. Studies show that filtration through a 5 micron filter needle sufficiently removes these particles.

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NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

VASOPRESSIN ANTAGONIST

FDA Recommends Against Prolonged Use of Magnesium Sulfate to Stop Pre-term Labor Due to Bone Changes in Exposed Babies

5/30/2013

FDA identified and reviewed case reports as well as epidemiologic data that show calcium and skeletal abnormalities in neonates whose mothers received magnesium sulfate for more than 5-7 days during pregnancy. Calcium and bone outcomes associated with a shorter duration of treatment are not known. Laboratory values resolved within days of birth, but long-term bone effects remain unknown due to short follow-up periods. This has resulted in a change in the drug label for Magnesium Sulfate Injection, USP 50%, including:

- a new *Warning* stating the administration of magnesium sulfate injection exceeding 5-7 days in pregnancy for the treatment of pre-term labor can lead to low calcium and bone changes in the baby;
- a new *Teratogenic Effects* section changing the Pregnancy Category to D (denoting a positive evidence of human fetal risk); and
- a new *Labor and Delivery* section stating that continuous administration of magnesium sulfate injection to treat pre-term label is not an approved use and that safety and efficacy for this purpose is not established.

CENTRAL NERVOUS SYSTEM

FDA Drug Safety Communication: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR

5/14/2013 ***** UPDATE FROM 01/10/2013*****

FDA has approved updated labeling changes reflecting lower dosing recommendations as well as warnings and precautions for zolpidem products (Ambien, Ambien CR, and Edluar) due to risk of next-morning impairment as discussed in a previous FDA Drug Safety Communication from January 2013. Patients who take zolpidem extended-release (Ambien CR)—either 6.25 mg or 12.5 mg—should not drive or perform activities requiring mental alertness the day after taking the drug due to high enough residual zolpidem levels that may impair these activities. New dosing recommendations include:

PRODUCT	NEW DOSING RECOMMENDATIONS FOR ZOLPIDEM (NON-ELDERLY ADULTS)
Ambien, Edluar, Zolpimist	**Women:** 5 mg once daily, immediately before bedtime **Men:** 5 or 10 mg once daily, immediately before bedtime
Ambien CR	**Women:** 6.25 mg once daily, immediately before bedtime **Men:** 6.25 or 12.5 mg once daily, immediately before bedtime

FDA Drug Safety Communication: Valproate Anti-seizure Products Contraindicated for Migraine Prevention in Pregnant Women due to Decreased IQ Scores in Exposed Children

5/6/2013 *****UPDATE FROM 06/30/2011*****

Stronger warnings with regard to valproate use will be added to the drug labels based on final results of the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study which showed that exposure to the anti-seizure medication valproate sodium or related products (valproic acid and divalproex sodium) at any time during pregnancy significantly lowers IQs in children at 6 years of age when compared to exposure to other select antiepileptic drugs during pregnancy. FDA recommends that manufacturers update product labeling to include the following risk information:

- Valproate sodium and related products, valproic acid and divalproex sodium, are contraindicated in pregnant women for the prevention of migraine headaches;
- Valproate's pregnancy category for migraine use will be changed from "D" (potential acceptable benefit despite potential risks) to "X" (risk outweighs any possible benefit of the drug in pregnant women);
- Valproate products will remain in pregnancy category D for treating epilepsy and manic episodes associated with bipolar disorder and should only be prescribed if other medications are not effective or unacceptable.

FDA advises health care practitioners to counsel women of childbearing age or planning a pregnancy using valproate products about:

- The increased risk for decreased IQ in children exposed to valproate products in utero;
- Other risks of valproate use during pregnancy (i.e., structural and functional birth defects like neural tube defects) and the recommendation for folic acid supplementation; and
- The **North American Anti-Epileptic Drug Pregnancy Registry** (http://www.aedpregnancyregistry.org/) to help quantify adverse drug events and major malformations in infants exposed to anti-epileptic drugs during pregnancy.

ONCOLOGY

FDA warns about potential medication errors resulting from confusion regarding nonproprietary name for breast cancer drug Kadcyla (ado-trastuzumab emtansine)

5/6/2013

FDA and ISMP described the potential for confusion between HERCEPTIN® [trastuzumab] and KADCYLA™ [ado-trastuzumab emtansine] due to similar generic names and indications for breast cancer. Since these drugs have different dosing and treatment schedules, look-alike/sound-alike name pair confusion could lead to possible dosing errors and potential patient harm. Both agents are associated with safety concerns if one is inadvertently administered instead of the other: KADCYCLA includes a boxed warning for hepatotoxicity, cardiac toxicity, and embryo-fetal toxicity; while HERCEPTIN includes a boxed warning for cardiomyopathy; infusion reactions and pulmonary toxicity; and embryo-fetal toxicity. Further details are included on pages 1 and 3.

Getting the most from our safety surveillance

OLMESARTAN AND CASE REPORTS OF SPRUELIKE ENTEROPATHY

In VA, the angiotensin II receptor antagonist (ARB) olmesartan is available non-formulary, and comprises approximately 0.04% of the utilization of the eight available ARBs. According to VA ADERS, there has been one report of severe diarrhea and vomiting that resolved upon discontinuation of olmesartan. Olmesartan was held due to the possibility of spruelike enteropathy.

The literature reports twenty-three cases of spruelike enteropathy and severe diarrhea resolving after discontinuation of olmesartan.[1,2] Twenty-two of these cases were described in the August 2012 issue of the Mayo Clinic Proceedings.[2] Referral diagnosis was nonresponsive/refractory celiac disease in 10 patients and unexplained sprue in 6 patients. According to information available in 14 of the patients, the mean duration of treatment with olmesartan prior to symptom onset was 3.1 years (range 0.5 to 7 years); and in 5 others, the patients had been taking olmesartan for at least 1 year prior to symptom onset. Diarrhea and weight loss were reported in all patients with a median stool frequency of 6 per day (range 3 to 42 per day) and median weight loss of 18 kg (range 2.5 to 57 kg). Villous atrophy with mucosal inflammation was evident upon baseline intestinal biopsy in all patients, with subepithelial collagen deposition seen in 7 patients. Upon discontinuation of olmesartan, it was reported that all patients experienced clinical response. Histologic recovery of the duodenum was observed in 17 of the 18 patients where a follow-up biopsy was performed (mean 8 months; range 54 to 707 days).[2]

The mechanism for this potential adverse effect with olmesartan is unclear; although it has been proposed to be related to potential interference with immune homeostasis in the gastrointestinal tract.[1,2] It is also unknown if enteropathy is potentially associated with use of the other ARBs.[1,2] It is unknown at this time if there is a definite association with olmesartan and spruelike enteropathy; however, until additional information is available, providers should consider this in the evaluation of patients prescribed olmesartan presenting with severe diarrhea.

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2. Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc 2012;87:732-8.

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Helping to achieve safe medication use

HERCEPTIN® [TRASTUZUMAB] AND KADCYLA™ [ADO-TRASTUZUMAB EMTANSINE]: POTENTIAL LOOK-ALIKE/SOUND-ALIKE NAME PAIR CONFUSION

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hepatotoxicity (liver failure and death), cardiac toxicity (reduction in left ventricular ejection fraction), and embryo-fetal toxicity (death or birth defects).

HERCEPTIN® [trastuzumab] is a HER2/neu receptor antagonist indicated:

- For the treatment of HER2 overexpressing breast cancer as monotherapy or adjuvant therapy.
- As combination therapy to treat HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

HERCEPTIN® [trastuzumab] is prescribed in doses up to 8 mg/kg per loading dose given via intravenous infusion, followed by a maintenance dose of 6mg/kg every 3 weeks – about twice the maximum dose of KADCYLA™ [ado-trastuzumab emtansine]. Safety concerns associated with HERCEPTIN® [trastuzumab] include a boxed warning for cardiomyopathy; infusion reactions and pulmonary toxicity (anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome within 24 hours of administration); and embryo-fetal toxicity (pulmonary hypoplasia, skeletal abnormalities, and neonatal death).

FDA as well as the National Medication Errors Reporting Program operated by the Institute of Safe Medication Practices (ISMP) recommends that health care practitioners:

- Increase awareness about the potential for confusion between HERCEPTIN® [trastuzumab] and KADCYLA™ [ado-trastuzumab emtansine] due to their similar generic names.
- Use the correct generic name. For example, if the nonproprietary name for KADCYLA™ [ado-trastuzumab emtansine] is incorrectly identified as "trastuzumab emtansine" in computerized order entry systems, manually correct the nonproprietary name for KADCYLA™ to "ado-trastuzumab emtansine".
- List KADCYLA™ by its full generic name [ado-trastuzumab emtansine] including the prefix and dash in information systems.
- Differentiate between the generic names to warn against confusion.
- Include brand and generic names when communicating printed or computerized medication orders.

ISMP has contacted major drug information vendors and major drug wholesalers to confirm proper use of the nomenclature.

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1. FDA Drug Safety Communication. FDA warns about potential medication errors resulting from confusion regarding nonproprietary name for breast cancer drug Kadcyla (ado-trastuzumab emtansine). http://www.fda.gov/downloads/Drugs/DrugSafety/UCM350735.pdf . Accessed 05/06/2013.
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4. KADCYLA™ (ado-trastuzumab emtansine) [prescribing information]. South San Francisco, CA: Genentech, Inc.; February 2013.
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