



▶ DABIGATRAN ETEXILATE MESYLATE (PRADAXA®) STORAGE AND HANDLING REQUIREMENTS 1



▶ MEDICATION SAFETY NEWS FROM THE VA NATIONAL PHARMACY BENEFITS MANAGEMENT SERVICES [PBM] AND THE FOOD AND DRUG ADMINISTRATION [FDA]..... 2-4



▶ G6PD DEHYDROGENASE DEFICIENCY AND HEMOLYTIC EVENTS .. 5



VA Center for Medication Safety

○ ISSUE 1 | ○ VOLUME 1 | ○ JUNE 2011

Medication *safety in seconds*

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

Helping to achieve safe medication use

DABIGATRAN ETEXILATE MESYLATE (PRADAXA®) STORAGE AND HANDLING

Healthcare professionals and patients are reminded of special storage and handling requirements for the dispensing and stocking of dabigatran etexilate mesylate (Pradaxa®), which is available in 30-day supply bottles and unit-dose blister packs. Dabigatran etexilate mesylate (Pradaxa®) hydrolyzes in humid/moist conditions, which deactivates the agent. Original manufacturer packaging minimizes the exposure to humidity and moisture; and dabigatran etexilate mesylate (Pradaxa®) must remain in original packaging to maintain potency (i.e., **capsules should not be placed in pill reminder boxes**). The original dabigatran etexilate mesylate (Pradaxa®) product labeling recommends use of the product within 30 days of

opening the package/bottle; however, new FDA data show no significant loss of potency up to 60 days after the bottle is opened as long as dabigatran etexilate mesylate (Pradaxa®) capsules remain in the original bottle with proper handling requirements practiced. Boehringer Ingelheim Pharmaceuticals, Inc., the manufacturer of dabigatran etexilate mesylate (Pradaxa®), has started a campaign to educate healthcare professionals (prescribers and pharmacists) about these requirements. Dabigatran etexilate mesylate (Pradaxa®) VA Criteria for Use are available on the PBM website in the Clinical Guidance Section under Criteria for Use.



NEWS YOU CAN USE

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

- ADDENDUM: Smith & Nephew Various Adhesive Remover Wipes and Potential Contamination Recall – [National PBM Communication](#) – 05/31/2011
- Nitroglycerin Tablets and Packaging Error Recall - [National PBM Communication](#) - 05/25/2011
- Smith & Nephew Various Adhesive Remover Wipes and Potential Contamination Recall - [National PBM Communication](#) - 05/20/2011
- Marcaine Incorrect Labeling and Potential Look-Alike Confusion - [National PBM Bulletin](#) - 05/13/2011
- Warfarin and High Potency Recall - [National PBM Communication](#) - 05/12/2011
- Citalopram and Finasteride Recall Due to Mislabeling [National PBM Communication](#) – 03/31/2011

NEWS YOU CAN USE

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

(continued from page 1)

- Povidine® Iodine Prep Pads and Potential Microbial Contamination Recall [National PBM Communication](#) – 03/29/2011
- Dexamethasone Sodium Phosphate Inj USP 4mg/ml and Particulate Formation Recall [National PBM Communication](#) – 03/23/2011
- PPIs: Long-Term Use and Risk of Hypomagnesemia [National PBM Communication](#) - 03/11/2011
- Dicyclomine and Doxycycline Look-Alike Sound-Alike (LASA) Confusion [National PBM Bulletin](#) - 03/10/2011
- Maternal and Newborn Risks with Certain Medications Used During Pregnancy [National PBM Communication](#) - 03/09/2011
- Albuterol Sulfate Inhalation Solution Recall- Packaging Error [National PBM Communication](#) – 02/11/2011
- Dronedaraone and Liver Injury [National PBM Communication](#) - 01/27/2011
- Triad Group Recall – Sterile Lubricating Jelly and Alcohol Swabs [National PBM Communication](#) - 01/20/2011

NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

[Drospirenone - Safety Review of possible increased risk of blood clots with birth control pills containing drospirenone](#)

05/31/2011

Two new studies state up to three-fold greater risk of venous thromboembolic events (VTE, including DVTs and PEs) in women who take drospirenone-containing oral contraceptives compared to levonorgestrel products. Previous studies had conflicting findings: two postmarketing studies did not reveal any difference in VTE risk between drospirenone-and levonorgestrel-containing agents or other progestins; however, two other publications showed up to two-fold higher VTE risk when women used drospirenone-containing contraceptives as opposed to levonorgestrel counterparts. FDA is currently reviewing all available information to assess the risk potential of VTE in women using oral contraceptives with drospirenone, including data from an additional FDA-sponsored study on hormonal contraceptives and associated thrombotic events, as well as risks, with results expected later this summer.

[Rosiglitazone - Updated Risk Evaluation and Mitigation Strategy \(REMS\) to Restrict Access to Rosiglitazone-containing Medicines including Avandia, Avandamet, and Avandaryl](#)

5/18/2011

New restrictions to the prescribing and use of rosiglitazone-containing medicines are based on data that suggested an elevated risk of heart attacks in patients treated with rosiglitazone and now includes a restricted access and distribution program which limits use to:

- Patients already receiving treatment with rosiglitazone-containing medicines; and
- Patients that have suboptimal control of blood sugar with other anti-diabetic medicines and refuse pioglitazone-containing medicines (Actos, Actoplus Met, Actoplus Met XR, or Duetact).

Patients and providers need to enroll in the Avandia-Rosiglitazone Medicines Access Program in order to receive their medicine by mail order through specially certified pharmacies participating in the program.

[Glass Syringe - Connection problems involving certain needleless pre-filled glass syringes containing adenosine and amiodarone](#)

5/6/2011

FDA received fifty-seven reports involving adenosine and five reports related to amiodarone needleless pre-filled glass syringes malfunctioning upon connection of the syringe to the pin-activated needleless IV access systems. This may cause the pin in the access system to clog or break off in the syringe tip, resulting in: prevention of delivery of the medication; damage to the IV tubing and/or the needleless access system; and reestablishment of IV access. Cases indicated life-threatening outcomes from inadequate administration of the medication to patients in emergency situations. FDA recommends stocking crash carts, ambulances, and emergency rooms with vials or pre-filled plastic syringes of adenosine and amiodarone.

[Tysabri - Safety update on Progressive Multifocal Leukoencephalopathy \(PML\) associated with Tysabri \(natalizumab\)](#)

04/22/2011

Product label updates include new information on PML incidence (102 cases of PML among 82,732 natalizumab [Tysabri] patients worldwide through February 28, 2011) and risk factors (greater risk in patients with past immunosuppressant use prior to receiving natalizumab [Tysabri], as well as in patients who have received more than 24 natalizumab [Tysabri] infusions).

[LABA - FDA requires post-market safety trials for Long-Acting Beta-Agonists \(LABAs\)](#)

04/15/2011

Five double-blind, controlled clinical trials that will further evaluate the safety of Long-Acting Beta-Agonists (LABAs) when used in combination with inhaled corticosteroids for the treatment of asthma will begin in 2011 and FDA expects to receive results in 2017.

[TNF Blockers - Safety Review update on reports of Hepatosplenic T-Cell Lymphoma in adolescents and young adults receiving tumor necrosis factor \(TNF\) blockers, azathioprine and/or mercaptopurine](#)

04/14/2011

Hepatosplenic T-Cell Lymphoma (HSTCL) continues to occur primarily in adolescents and young adults with Crohn's disease and ulcerative colitis receiving treatment with tumor necrosis factor (TNF) blockers, as well as with azathioprine, and/or mercaptopurine, alone or in combination with TNFs, as per reports to the FDA Adverse Event Reporting System (AERS), as well as in the literature and in the HSTCL Cancer Survivors' Network.

NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

(continued from page 2)

[Olmesartan - Safety Review Update of Benicar \(olmesartan\) and cardiovascular events](#)

04/14/2011

In June 2010, FDA reviewed two long-term clinical trials and found that patients with type 2 diabetes taking olmesartan (Benicar) for blood pressure control had a higher rate of cardiovascular-related death compared to patients taking a placebo. After further review of the two trials and the total clinical trial data on olmesartan (Benicar), FDA determined that the benefits of olmesartan (Benicar) outweigh its potential risks when used for the treatment of patients with high blood pressure.

[Revlimid - Ongoing safety review of Revlimid \(lenalidomide\) and possible increased risk of developing new malignancies](#)

04/08/2011

Preliminary data from US and international controlled clinical trials of lenalidomide (Revlimid) show an increased incidence of some second primary malignancies, particularly acute myelogenous leukemia (AML) and B-cell lymphoma malignancies, when compared to controls after prolonged drug exposure. However, FDA does not recommend delaying, modifying, or restricting the use of lenalidomide (Revlimid) for patients being treated according to the FDA-approved indications while the agency continues its investigations.

[Benzocaine sprays - FDA continues to receive reports of serious and potentially fatal adverse effects with the use of benzocaine sprays for medical procedures](#)

04/07/2011

FDA first announced the association of methemoglobinemia with the use of benzocaine sprays during medical procedures in a Public Health Advisory released in June 2006. FDA has since received reports of additional cases of methemoglobinemia (72), of which three resulted in death, associated with the use of benzocaine sprays.

[Benzocaine gels and liquids - Reports of serious and potentially fatal adverse effects with the use of over-the-counter \(OTC\) benzocaine gels and liquids applied to the gums or mouth](#)

04/07/2011

Over-the-counter (OTC) benzocaine preparations include gels and liquids (i.e., Anbesol, Hurricaine, Orajel, Baby Orajel, Orabase, and store brands), as well as lozenges and spray solutions. Methemoglobinemia occurred with all strengths of benzocaine gels and liquids, especially in children two years of age or younger treated for teething. Symptoms may include discoloration (blue, gray, or pale appearance) of skin, lips, and nail beds; shortness of breath; fatigue; confusion; headache; lightheadedness; and rapid heart rate.

[FDA Drug Safety Communication: Special storage and handling requirements must be followed for Pradaxa \(dabigatran etexilate mesylate\) capsules](#)

03/29/2011

Dabigatran etexilate mesylate (Pradaxa®) product labeling recommends use of the product within 30 days of opening the package/bottle. FDA data show no significant loss of potency up to 60 days after the bottle is opened as long as dabigatran etexilate mesylate (Pradaxa®) capsules remain in the original bottle with proper handling requirements practiced.

[PPI Update - Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors](#)

03/24/2011

Data reviewed by the FDA shows minimal risk of fracture with short-term, low dose PPI use. Those at highest risk for fractures received high doses of prescription PPIs and/or use a PPI for a prolonged duration of one year or more.

[Kaletra - Serious health problems seen in premature babies given Kaletra \(lopinavir/ritonavir\) oral solution](#)

03/08/2011

Lopinavir/ritonavir (Kaletra) oral solution contains alcohol and propylene glycol, which can accumulate in a neonate due to suboptimal elimination of propylene glycol, leading to an increased risk of propylene glycol-associated adverse events. Data from FDA AERS revealed 10 post-marketing cases in neonates, with life-threatening events reported. Symptoms consisted of: cardiac toxicity (bradycardia, sinoatrial block, complete AV block, congestive cardiomyopathy, cardiac failure, and cardiogenic shock); an elevated lactate level; neuromuscular toxicity (hypotonia, an abnormal EEG, altered state of consciousness, somnolence, and asthenia); acute renal failure and an increased serum creatinine; hyperkalemia; respiratory complications (respiratory failure, pulmonary hemorrhage, neonatal respiratory arrest, dyspnea and wheezing); gastrointestinal adverse events (vomiting, abdominal distention, and ulcerative colitis), and failure to thrive. There was one death among the ten infants. FDA noted that the majority of these cases occurred outside the U.S.

[Letairis - Liver injury warning to be removed from Letairis \(ambrisentan\) tablets](#)

03/04/2011

New data reviewed by the FDA shows a low risk of hepatotoxicity with ambrisentan (Letairis), reflected in the revised label that removes this safety issue from the boxed warning. Product will still be prescribed and dispensed via the Letairis Education and Access Program (LEAP), and monthly monitoring of serum liver enzymes is no longer required for drug use and access.

[Topamax - Risk of oral clefts in children born to mothers taking Topamax \(topiramate\)](#)

03/04/2011

Topiramate (Topamax) changed classifications from Pregnancy Category C to Pregnancy Category D due to new human data that show an increased risk for oral clefts in infants born to women treated with topiramate (Topamax and generic products) during pregnancy.

[PPIs - Low magnesium levels can be associated with long-term use of Proton Pump Inhibitor drugs \(PPIs\)](#)

03/02/2011

FDA reviewed 38 reports from the Adverse Event Reporting System (AERS) and 23 cases from the medical literature (8 cases overlapped), but the available data are insufficient to quantify an incidence rate for hypomagnesemia with PPI therapy. Onset of hypomagnesemia occurred after at least 3 months to more than a year of therapy. Serious adverse events included tetany, seizures, tremors, carpo-pedal spasm, atrial fibrillation, supraventricular

MUES AND MUETS

NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

(continued from page 3)

tachycardia, abnormal QT interval, and concomitant hypocalcemia in light of normal parathyroid hormone levels. The mechanism for hypomagnesemia with long term PPI use remains unclear, but could be related to altered intestinal absorption of magnesium. Treatment of hypomagnesemia may necessitate magnesium supplementation as well as discontinuation of the PPI.

[Abacavir - Safety Review update of Abacavir and possible increased risk of heart attack](#)

03/01/2011

A conflict in existing information shows an increased risk of heart attack (myocardial infarction or MI) with abacavir in several observational studies and one randomized controlled trial (RCT) while other RCTs and the safety database maintained by the drug manufacturer do not observe this outcome. FDA conducted a meta-analysis of 26 RCTs which did not show an increased risk of heart attack.

[Antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns](#)

02/22/2011

FDA updated the *Pregnancy* section of drug labels for the entire class of antipsychotic drugs with information about possible abnormal muscle movements (i.e., extrapyramidal signs or EPS) and withdrawal symptoms in newborns whose mothers received antipsychotic medications (Table 1) during the third trimester of pregnancy. 69 cases of neonatal EPS or withdrawal with all antipsychotic drugs were reported to FDA's Adverse Event Reporting System (AERS) database through October 29, 2008. Symptoms included: agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder. Onset of symptoms occurred from birth to one month after birth. Severity of symptoms ranged from recovery within hours or days without specific treatment to prolonged hospitalization requiring intensive care unit support, with administration of phenobarbital and benzodiazepines to alleviate withdrawal symptoms.

[Terbutaline - New warnings against use of terbutaline to treat preterm labor](#)

02/17/2011

FDA is requiring the addition of a *Boxed Warning* and *Contraindication* to the terbutaline injection label, as well as the terbutaline oral tablet label, stating that:

- *injectable terbutaline should not be used in pregnant women for prevention or prolonged treatment (beyond 48-72 hours) of preterm labor in either the hospital or outpatient setting because of the potential for serious maternal heart problems and death; and*
- *oral terbutaline should not be used for prevention or any treatment of preterm labor because it has not been shown to be effective and has similar safety concerns.*

[Avandia - Avandia \(rosiglitazone\) labels now contain updated information about cardiovascular risks and use in certain patients](#)

02/03/2011

In September 2010, FDA restricted the prescription and use of rosiglitazone (Avandia) due to cardiovascular risks (including heart attack). Revised product labels reserve the use of rosiglitazone and rosiglitazone-containing medications for patients: already being treated with these medicines; and/or whose blood sugar cannot be controlled with other anti-diabetic medicines and who, after consulting with their healthcare professional, do not wish to use pioglitazone-containing medicines (Actos, Actoplus Met, Actoplus Met XR, or Duetact). Approval and implementation of the Risk Evaluation and Mitigation Strategy (REMS) will limit the availability of rosiglitazone-containing medicines.

[Multaq \(dronedarone\) - Severe liver injury associated with the use of dronedarone \(marketed as Multaq\)](#)

01/14/2011

In January 2011, FDA received case reports of liver injury and failure in patients treated with dronedarone. Two post-marketing reports of acute hepatic failure requiring transplantation have been documented. The Warnings and Precautions and Adverse Reactions sections of the product labeling for dronedarone are currently being revised to include information on the risk for potential liver injury. FDA recommends initial monitoring of liver function during the first 6 months of treatment and to discontinue therapy (with no rechallenge) if liver injury is suspected.

[Acetaminophen - Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure](#)

01/13/2011

The FDA is limiting the maximum amount of acetaminophen in a prescription unit (tablet, capsule, etc.) to 325 mg in order to reduce the risk of liver injury or overdose associated with acetaminophen and/or acetaminophen-containing products. This will not affect the quantity of tablets or capsules prescribed per dose and/or the interval between doses.

[Lantus - Update to ongoing safety review of Lantus \(insulin glargine\) and possible risk of cancer](#)

01/12/2011

In July 2009, FDA began to review four published observational studies, of which three implied an increased risk of cancer associated with the use of insulin glargine (Lantus). However, methodological limitations of these studies prevent a clear conclusion from being drawn regarding the risk of cancer with insulin glargine (Lantus). Three epidemiological studies conducted by the manufacturer will further evaluate cancer risk associated with the use of insulin glargine (Lantus) with results expected by the end of June 2011.

A Medication Use Evaluation (MUE) is a performance improvement method that focuses on evaluating and improving medication-use processes with the goal of improving patient outcomes.

VAMedSAFE has developed a Medication Use Evaluation Tracker (MUET) to facilitate the MUE process. The goals of MUET are:

1) to provide VA medical centers across the country with secured lists of target patients that meet pre-set criteria for intervention, and

2) to enable these interventions to be "written back" into a "live" centralized database.

Ongoing initiatives

include:

Amiodarone

ESAs

Glyburide

For facility-level MUET training within your network, please contact:

Muriel Burk, Pharm.D.,
at Muriel.Burk@va.gov;

or

Von Moore, Pharm.D.,
at Von.Moore@va.gov.



Getting the most from our safety surveillance

GLUCOSE - 6 - PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY AND HEMOLYTIC EVENTS

In February 2011, a report was submitted to the VA Adverse Drug Event Reporting System (VA ADERS) involving the administration of one dose of rasburicase to a cancer patient. Hemolysis developed. The patient expired and was later found to be G6PD deficient.

G6PD deficiency is the most common enzymatic disorder of red blood cells in humans and is estimated to affect 400 million worldwide. G6PD deficiency primarily affects individuals of African, Mediterranean, and Asian descent. The condition is an X-linked defect where G6PD enzymatic activity is reduced.

G6PD catalyzes the first rate-limiting step in the pentose phosphate pathway of glycolysis. The importance of this step is the production of nicotinamide adenine nucleotide phosphate (NADPH), which is essential in the protection of red blood cells from oxidative damage.¹⁻⁴ The severity of deficiency is indicated by the magnitude of enzymatic activity:

- Class I – severe enzyme deficiency of <10% of normal and have chronic hemolytic anemia;
- Class II – severe enzyme deficiency, but there is usually only intermittent hemolysis;
- Class III – moderate enzyme deficiency of 10-60% of normal with intermittent hemolysis associated with drugs or infection;
- Class IV – no enzyme deficiency or hemolysis;
- Class V – increased enzyme activity.

Individuals with G6PD deficiency are asymptomatic but can develop acute hemolysis due to oxidative stress from certain triggers. Common precipitants include: infection, oxidative drugs, and ingestion of certain foods (such as fava beans).

Currently, there is no substantial literature identifying causative agents in individuals developing hemolysis due to G6PD deficiency. The FDA maintains a webpage of approved drugs with pharmacogenomic information contained in the drug label. At this time, three drugs associated with G6PD deficiency appear on this webpage: chloroquine, dapsone, and rasburicase. The webpage can be found at <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm0833378.htm>.⁵

Select drugs that should be avoided in patients with G6PD deficiency*

GENERIC NAME	HEMOLYSIS-RELATED VA ADERS REPORTS
ACETANILIDE	NO
DAPSONE	YES
METHYLENE BLUE	NO
PHENAZOPYRIDINE	YES
PRIMAQUINE	YES
RASBURICASE	YES
SULFAMETHOXAZOLE	YES
SULFACETAMIDE	NO
SULFANILAMIDE	NO
SULFAPYRIDINE	NO

*This list is comprised of specific medications that should be avoided in patients with G6PD deficiency found in the literature^{6,7} and have seen usage in the VA system within the last five fiscal years. This list is not all-inclusive.

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Contributed by: Anthony Au, Pharm.D.,
PGY-2 Resident

PROVIDER RECOMMENDATIONS: Benefit vs.Risk



Before prescribing drugs that cause oxidative stress, providers may consider further inquiry about prior episodes of hemolytic anemia precipitated by drugs, infection or other precipitants (diabetic ketoacidosis, certain foods), especially for patients at high risk of being G6PD deficient.

Patient populations at high risk of being G6PD deficient are men of African, Mediterranean (especially of Kurdish Jewish descent), or Asian descent;

Routine screening for G6PD Deficiency in at risk patients is not typically recommended. Screening may be considered in the following groups:

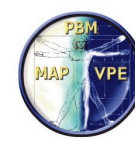
- High risk populations (e.g., those of Kurdish Jewish descent)
- Patients who are suspected to have a deficiency by their clinical history (e.g., a prior unexplained episode of hemolytic anemia).
- HIV positive patients with predisposing racial or ethnic background that may require opportunistic infection prevention prophylaxis as recommended by Infectious Disease Society of America.⁸
- Centers for Disease Control and Prevention recommends G6PD deficiency testing in patients prior to starting primaquine in treating malaria.⁹



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



VA Center for Medication Safety