VA Center for Medication Safety

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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

PRIMATENE MIST ® PHASE-OUT AS OF DECEMBER 31, 2011

Epinephrine inhalers containing chlorofluorocarbon (CFC) propellants, marketed as Primatene Mist ®, have been phased-out and are no longer available for purchase as of December 31, 2011. This results from an international agreement called *The Montreal Protocol on Substances that Deplete the Ozone Layer*, which makes illegal the production, distribution, and sale of substances that decrease the ozone layer, including CFCs. Primatene Mist ®, the only over-the-counter (OTC) asthma inhaler sold in the United States, aids in the temporary relief of occasional symptoms of mild asthma. Since the phase-out only applies to the manufacture and sale of CFC inhalers, patients may still use any remaining Primatene Mist® until the product expiration date. Providers with patients that use Primatene Mist ® should consider:

- Notifying their patients of the phase-out of Primatene Mist® and the unavailability of other OTC or prescription epinephrine inhalers without the CFC propellant;

- Determining an alternate treatment option to manage mild asthma symptoms (if indicated);
- Educating patients on the technique and proper use of inhaler medications.

REFERENCES:

1. FDA Drug Safety and Availability: Epinephrine CFC Metered-dose Inhalers - Questions and Answers. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm080427.htm . (Accessed 01/10/12).
2. FDA Drug Safety and Availability: Phase-Out of Epinephrine CFC Metered-Dose Inhalers—Primatene Mist With Chlorofluorocarbons No Longer Available After Dec. 31, 2011. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm193304.htm . (Accessed 01/10/12).
3. FDA Consumer Update: Primatene Mist With Chlorofluorocarbons No Longer Available After Dec. 31, 2011. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm247196.htm . (Accessed 01/10/12).
4. The Montreal Project on Substances that Deplete the Ozone Layer. http://www.unep.org/ozone/Montreal-Protocol/Montreal-Protocol2000.shtml . (Accessed 01/10/12).

NEWS YOU CAN USE

FROM THE FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

Acetaminophen - Addition of another concentration of liquid acetaminophen marketed for infants

12/22/2011

Manufacturers have made available a less concentrated liquid acetaminophen product (160 mg/5 ml) marketed for infants due to dosing errors reported with the 80 mg/0.8 mL and 80 mg/1 mL concentrations. Packaging for the 160 mg/5 mL acetaminophen product marketed for infants may include an oral syringe instead of a dropper. Manufacturers advise to use only the dosing device provided with the product. The Drug Facts

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NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

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label on the package shows product concentration (in mg/mL), dosage, and directions for use to avoid the potential for dosing errors/confusion.

Gilenya - Safety review of a reported death after the first dose of Multiple Sclerosis drug Gilenya (fingolimod)
12/20/2011
The FDA has alerted practitioners and providers to a report in FDA's Adverse Events Reporting System (AERS) database describing the death of a patient with multiple sclerosis (MS) within 24 hours of taking the first dose of fingolimod (GILENYA). This patient had completed, without incident, a 6-hour monitoring period following initial administration of the agent. The report documents this patient receiving a beta blocker (metoprolol) and a calcium channel blocker (amlodipine). At present, the cause of death is not known.

Fingolimod (GILENYA) is a sphingosine-1-phosphate-receptor modulator which may induce a decrease in heart rate and/or an atrioventricular conduction block. In clinical trials, this occurred within six hours of the initial fingolimod (GILENYA) dose, thus necessitating inclusion of a monitoring period in the drug labeling. Additionally, a published case report describes the development of a 7-second period of asystole and sustained bradycardia 21 hours after the first fingolimod (GILENYA) dose in a 20-year old patient. The patient concurrently received risperidone which may have contributed to these effects as well. †

FDA recommendations include a baseline EKG in patients with a possible risk for bradyarrythmias, including patients who are also prescribed antiarrhythmic drugs (Class Ia or Class III), beta blockers, calcium channel blockers, as well as those with a low heart rate, history of syncope, sick sinus syndrome, 2nd degree or higher conduction block, ischemic heart disease, or congestive heart failure.* FDA continues to evaluate this case and believes that fingolimod (GILENYA) confers clinical benefit when used as directed.

*† **[ADDITIONAL REFERENCE FOR PUBLISHED CASE REPORT:** Espinosa PS, Berger JR. Delayed fingolimod-associated asystole. Mult Scler. 2011 Nov;17(11):1387-9.]*

**** [NOTE: Fingolimod (GILENYA) has not been studied in patients with ischemic heart disease, congestive heart failure, 2nd degree or higher conduction block, sick sinus syndrome, or prolonged QT interval. In addition, no studies evaluated the use of fingolimod (GILENYA) with Class Ia or Class III antiarrhythmic agents.]***

Contributed by: Kathryn Tortorice, Pharm.D., B.C.P.S.

Multaq - Review update of Multaq (dronedarone) and increased risk of death and serious cardiovascular adverse events
12/19/2011 ***** UPDATE FROM 07/21/2011 *****
Dronedarone (MULTAQ) is currently indicated to reduce hospitalization for atrial fibrillation (AF) in patients in sinus rhythm with a history of non-permanent AF (paroxysmal or persistent AF). A completed review by the FDA finds that:

- Dronedarone (MULTAQ) increases the risk of serious cardiovascular (CV) events, including death, when used by patients in permanent AF, as reflected in the product label's updated boxed warning.
- Dronedarone provides a benefit for patients with non-permanent AF (i.e., paroxysmal AF: AF that terminates spontaneously within 7 days; or persistent AF: recurring episodes of AF lasting more than 7 days).

Additional labelling changes include warnings and recommendations that advise to:

- Avoid dronedarone (MULTAQ) in patients with AF unable to undergo conversion to normal sinus rhythm (permanent AF) since dronedarone (MULTAQ) doubles the rate of cardiovascular death, stroke, and heart failure in such patients.
- Monitor heart (cardiac) rhythm by electrocardiogram (ECG) at least once every 3 months. If the patient experiences AF, discontinue dronedarone (MULTAQ) or, if clinically indicated, cardiovert.
- Prescribe appropriate antithrombotic therapy for patients receiving dronedarone (MULTAQ) .

Zocor (simvastatin) - Revised dose limitation for Zocor (simvastatin) when taken with amiodarone
12/15/2011 ***** UPDATE FROM 06/08/2011 *****
In June 2011, FDA lowered the simvastatin dose limitation from 20 mg to 10 mg when taken concomitantly with amiodarone to avoid drug interaction. However, contrary to other interacting drugs, no pharmacokinetic or clinical trial data supported the decrease in simvastatin dose when used with amiodarone. Consequently, FDA restored the simvastatin dose limit to 20mg when taken with amiodarone.

SSRI - Selective serotonin reuptake inhibitor (SSRI) antidepressant use during pregnancy and reports of a rare heart and lung condition in newborn babies
12/14/2011
A single published study supported FDA's previous Public Health Advisory in 2006 warning about the use of SSRI antidepressants by women during pregnancy and the potential risk of persistent pulmonary hypertension of the newborn (PPHN). PPHN may potentially require intensive supportive care measures, with severe cases possibly resulting in multiple organ damage, including brain damage, and even death. Conflicting findings from newer studies that evaluate this potential risk make it difficult for FDA to definitively associate SSRI use in pregnancy with PPHN. Health care providers should continue to treat depression during pregnancy as clinically appropriate. FDA will update the SSRI labels as any new data regarding SSRI use and PPHN become available.

ADHD - Safety Review Update of Medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in adults
12/12/2011
Two large epidemiologic studies looked at increased risk of heart attack (myocardial infarction, or MI), sudden cardiac death, or stroke possibly associated with ADHD medications including stimulants (amphetamine products and methylphenidate), atomoxetine, and pemoline (no longer marketed). Data analyzed from one study that evaluated heart attacks and sudden deaths in a sample of adults, and a second study that examined strokes in these adults, did not reveal an increased risk of serious adverse cardiovascular events in adults taking the above products. FDA recommends continued use of ADHD medications, provided that:

- *Stimulant products and atomoxetine should generally not be used in patients with serious heart problems, or for whom an increase in blood pressure or heart rate would be problematic.*
- *Patients treated with ADHD medications should be periodically monitored for changes in heart rate or blood pressure.*

NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

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Pradaxa - Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate)
12/7/2011
FDA currently evaluates post-marketing reports of serious bleeding in patients taking dabigatran etexilate (PRADAXA) submitted to the Adverse Events Reporting System (AERS) database to determine whether the event occurs more commonly than observed in the large clinical trial that supported its approval. The review considers inappropriate dosing, use of interacting drugs, or other clinical factors that might lead to a bleeding event. Using dabigatran etexilate (PRADAXA) appropriately and according to the approved drug label optimizes clinical benefit.

Nplate and Promacta - Modified Risk Evaluation and Mitigation Strategies (REMS) for Nplate (romiplostim) and Promacta (eltrombopag)
12/6/2011
Romiplostim (NPLATE) [approved on August 22, 2008] and eltrombopag (PROMACTA) [approved on November 20, 2008] treats chronic immune (idiopathic) thrombocytopenia (ITP) suboptimally responsive to corticosteroids, immunoglobulins, or splenectomy. Originally, the small sample sizes and short durations of the clinical trials for approval of these drugs, as well as the absence of long-term safety data, necessitated a Risk Evaluation and Mitigation Strategies (REMS) program to ensure benefits with use exceeded risks. The REMS restricted distribution and called for additional safety monitoring, since pre-market clinical trials demonstrated possible adverse effects including bone marrow reticulin formation and fibrosis; progression of thrombocytopenia upon drug discontinuation; thromboembolic events; increased risk of hematological malignancies due to marrow stimulation effects; and possible hepatotoxicity [observed only with eltrombopag (PROMACTA)]. However, the adverse event data collected via REMS became challenging to interpret due to confounding by indication. As a result, FDA removed the requirements for restricted distribution and additional safety data collection so that health care providers/institutions, pharmacies, and patients do not need to register with the REMS programs in order to prescribe, dispense, or take these drugs.

Getting the most from our safety surveillance

DABIGATRAN ETEXILATE (PRADAXA®) MONITORING | OUTCOMES EVENTS AND SAFETY

Anticoagulant therapies carry a risk of bleeding that can lead to serious or even fatal outcomes. Dabigatran etexilate (Pradaxa®), a new anticoagulant used in minimizing the risk of stroke in patients with non-valvular atrial fibrillation (AF), contains a warning in its product labeling regarding significant and sometimes fatal bleeding complications. Gastrointestinal bleeding was more frequently reported with dabigatran compared to warfarin in the pivotal RE-LY trial. An FDA investigation currently examines post-marketing severe bleeding events with dabigatran to determine if rates lie within or above that observed in clinical trials. FDA does maintain that dabigatran provides an important clinical benefit when used as directed.

Because of the potential widespread use of dabigatran in the VA population, the lack of long-term safety data, and information outside of a clinical trial setting, the VA Center for Medication Safety (VA MedSAFE) regularly monitors dabigatran for safety and inappropriate use. Outcome events undergo adjustment for duration of exposure to dabigatran and comparison to new users of warfarin with atrial fibrillation (AF). Thus far, event rates for dabigatran remain low, making it difficult to draw firm conclusions from the data. Additionally, no cases of liver failure or intracranial bleeds surfaced. Results as of 09/30/11 indicate:

- Out of 1524 patients receiving dabigatran from VA:
  - 809 (53%) represented new users;
  - 715 (47%) switched from warfarin.
- Outcome events identified by coding included:
  - 16 gastrointestinal (GI) bleeds (8 new users, 8 switchers);
    - GI bleeds occurred more frequently in users of dabigatran compared to warfarin, but this finding did not appear statistically different.
    - The 95% confidence intervals between dabigatran and warfarin groups for GI bleeds overlap and remain fairly wide with dabigatran (given the overall small numbers of events).
  - 8 strokes (3 new users, 5 switchers);
  - 1 systemic embolism; and
  - 1 acute myocardial infarction.

Routine review of adverse drug event (ADE) reports submitted to the VA Adverse Drug Event Reporting System (VA ADERS) also occurs on a weekly basis. Of the 58 VA ADERS reports through 12/01/11 that identify dabigatran as the primary suspect drug:

- 21 severe events occurred.
  - GI bleeds that resulted in hospitalization and/or transfusion comprised most.
  - Cases with more information documented revealed several of these patients as elderly and/or with renal impairment.
- The majority of the mild ADEs reported included GI symptoms or headache.

Future surveillance monitoring will occur every 6 months, with VA ADERS reports review continuing every week. A dabigatran medication utilization evaluation tracker (MUET) will launch in February 2012, enabling providers to make interventions where inappropriate use exists.

REFERENCES:

1. FDA Drug Safety Communication: Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate). http://www.fda.gov/Drugs/DrugSafety/ucm282724.htm . Accessed 01/06/2012.
2. Pradaxa (dabigatran etexilate mesylate) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; March 2011.

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