



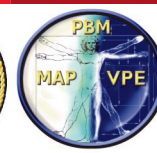
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VA Center for Medication Safety

○ ISSUE 3 | ○ VOLUME 2 | ○ MARCH 2012

# Medication safety in seconds

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

## Helping to achieve safe medication use



### STATIN DRUG CLASS: FDA-APPROVED LABELING UPDATES

In February 2012, the FDA announced safety-labeling changes for the statin drug class. The labeling changes resulted from a comprehensive review of the statin class by the FDA and included updated information regarding routine monitoring of liver enzymes in patients on statins; newly recognized adverse drug events for the statin class; and new contraindications and dose limitations for lovastatin when combined with certain medications. A summary of the labeling changes is discussed below.

**Monitoring Liver Enzymes:** Routine periodic monitoring of liver function tests is no longer recommended in patients receiving statin therapy. Based upon the evidence reviewed, the FDA concluded that liver toxicity with statins is rare and unpredictable and periodic monitoring does not appear to prevent or detect serious liver injury associated with statins. If signs and symptoms of liver injury manifest during statin therapy, the statin should be withheld and if another cause for the liver injury cannot be identified, the statin should not be restarted. *New recommendations include testing of liver enzymes at baseline (prior to statin use) and as clinically indicated thereafter. Routine, periodic testing is no longer recommended.*

**Adverse Events Associated with Statin Therapy now Included in Statin Labels:** Information regarding reported cases of non-serious, reversible cognitive impairment as well as impaired fast-

ing glucose, incident diabetes and increases in hemoglobin A1C (HbA1c) associated with statin therapy has been added to statin labels.

- **Cognitive adverse events**—From their review, the FDA noted that post-marketing reports of cognitive impairment typically occurred in patients older than 50 years who experienced reduced memory or loss of memory that resolved when the statin was discontinued. From this information, along with observational studies and clinical trials, the FDA concluded that the onset of cognitive impairment was quite variable (days to years of exposure), was not associated with a specific statin, age of the patient, statin dose or use of other concurrent medications. Furthermore, the data reviewed do not support impaired cognition as a common event or one that leads to clinically important declines in cognition during treatment with statins.
- **Impaired fasting glucose, incident diabetes and increased HbA1c**—Prompted in part by findings from two large clinical trials (*Justification for the Use of Statins in Primary Prevention [JUPITER]* and *Pravastatin and Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction*

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# NEWS YOU CAN USE

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

- Lo/Ovral-28 and Norgestrel/Ethinyl Estradiol Tablets - Recall for Inexact Tablet Counts or Out of Sequence Tablets - [National PBM Communication](#) – 02-03-2012

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# NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

## [Important safety label changes to cholesterol-lowering statin drugs](#)

02/28/2012

Revisions to the drug labels for the statin drug class include:

- A change in hepatic monitoring requirements; testing of liver enzymes before statin therapy and as clinically indicated thereafter will suffice instead of the previous routine/periodic monitoring.
- New adverse event information; cognitive adverse events (memory loss and/or confusion) and increases in glycosylated hemoglobin (HbA1c) as well as fasting plasma glucose have been observed/reported with statin use.
- Updates in lovastatin drug-drug interactions, contraindications, and dose limits; this will help to reduce the risk of potential adverse events (i.e., muscle injury) when combined with certain medications.

For more information, see “Statin Drug Class: FDA-Approved Labeling Updates” on page 1.

## [CardioGen-82 - Planned return of CardioGen-82 to market with new Boxed Warning](#)

02/15/2012 (\*\*\*) UPDATE FROM 01/12/2012 (\*\*\*)

CardioGen-82 will return to the U.S. market with revised FDA-approved labeling that includes a *Boxed Warning* regarding unintended radiation exposure when the levels of Sr-82 or Sr-85 in the rubidium Rb chloride injection exceed limits ; additional testing information for reducing the risk of exposure to unintended levels of strontium radiation; and instructions on how to identify expired generators and when to stop their use. For optimal results, providers should follow the directions in the new labeling.

## [Victrelis - Important drug interactions between Victrelis \(boceprevir\) and ritonavir-boosted human immunodeficiency virus \(HIV\) protease inhibitor drugs](#)

02/8/2012

Co-administration of boceprevir (Victrelis, a hepatitis C virus [HCV] protease inhibitor) and ritonavir-boosted human immunodeficiency virus (HIV) protease inhibitors atazanavir, lopinavir, and darunavir results in a drug interaction that can potentially reduce the effectiveness of each, making the use of their combinations not recommended. Boceprevir (Victrelis) is not indicated for use in patients with both HIV-1 and chronic HCV infections due to lack of safety and efficacy data in this coinfecting population. In the case of previously initiated coadministration, providers should closely monitor for HCV treatment response and for HCV and HIV virologic rebound.

## [Proton Pump Inhibitors - Clostridium difficile-associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors \(PPIs\)](#)

02/08/2012

Evidence from case reports submitted to FDA’s Adverse Drug Event Reporting System (AERS) as well as in the medical literature suggests a positive association between the use of PPIs and *Clostridium difficile* (*C. difficile*) infection and disease, including *C. difficile*-associated diarrhea (CDAD) [1.4 to 2.75 times higher risk in PPI-exposed patients compared to non-PPI-exposed patients]. Aside from PPI use, additional factors that may influence the risk of CDAD could include elderly age, chronic and/or concomitant underlying medical conditions, or broad spectrum antibiotic use. Limited data impedes further evaluation of the relationship between the risk of *C. difficile* infection or CDAD and prior PPI use, PPI dose and duration of use, and use of over-the-counter PPIs . Consider a diagnosis of CDAD in PPI users with diarrhea that does not improve, or abdominal pain and fever.

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# Helping to achieve safe medication use

STATIN DRUG CLASS: FDA-APPROVED LABELING CHANGES

(continued from page 1)

22 [PROVE-IT TIMI 22]) of a higher incidence of new diabetes or worsened glycemic control in the statin or high-dose statin group in each trial, the FDA reviewed the published literature and identified several meta-analyses and epidemiological data that supported an effect of statins on incident diabetes (1/1000 patient years [1 case of DM for every 255 patients treated for 4 years] in one meta-analysis involving over 90,000 patients) and increases in HbA1c and/or fasting plasma glucose.

Despite this new information, the FDA indicates that they “...continue to believe that the cardiovascular benefits of statins outweigh these small risks.”

**Lovastatin Drug Interactions:** Prompted by the updated simvastatin safety labeling in June 2011 (originating primarily from the SEARCH trial), the lovastatin label has been modified as well due to similar physiochemical and pharmacokinetic properties between lovastatin and simvastatin. The updated lovastatin label also includes new contraindications for lovastatin and more aggressive dose limits for lovastatin when combined with certain medications (See Table 1 on page 3).

# Getting the most from our safety surveillance



## PROCEDURAL ERROR LEADS TO MEDICATION ERROR

Two VA medical centers have reported a procedural error that led to a potential for patient harm. In both cases, the error occurred due to staff bypassing standard operating procedures resulting in no final check of a technician's work by a pharmacist.

According to one site report, a technician made a mistake re-packaging medications and did not obtain a final check from a pharmacist, resulting in the improper labeling and packaging of two medications: thiamine (a B-complex vitamin) as carbamazepine (an anti-epileptic medication used in managing seizures and other psychiatric disorders), and vice versa. The two medications, available in tablet form, appear similar. Out of twenty-one inpatients possibly affected by this error, five patients may have received thiamine instead of carbamazepine while sixteen patients may have received carbamazepine instead of thiamine.

Pharmacy Service implemented immediate corrective actions including checking all unit dose inventory to confirm correct medications; removing all pharmacy technicians from unit dose packaging duties until they have completed re-training in this procedure; and requiring closer oversight by a pharmacist for unit dose packaging. Both facilities documented no patient harm.

To prevent ongoing issues of this nature, pharmacy staff should take the opportunity to review their procedures and to conduct spot checks in order to ensure understanding and completion of all steps.

### REFERENCES

1. FIELD Information Report.

# Helping to achieve safe medication use

## STATIN DRUG CLASS: FDA-APPROVED LABELING CHANGES

(continued from page 2)

TABLE 1. LOVASTATIN : FDA-APPROVED LABELING CHANGES FOR CONTRAINDICATIONS, DOSE LIMITS, AND OTHER SPECIAL INSTRUCTIONS

PREVIOUS LOVASTATIN LABEL	NEW LOVASTATIN LABEL
<b>Avoid lovastatin with:</b> <ul style="list-style-type: none"> <li>• Itraconazole</li> <li>• Ketoconazole</li> <li>• Erythromycin</li> <li>• Clarithromycin</li> <li>• Telithromycin</li> <li>• HIV protease inhibitors</li> <li>• Nefazodone</li> </ul>	<b>Contraindicated with lovastatin:</b> <ul style="list-style-type: none"> <li>• Itraconazole</li> <li>• Ketoconazole</li> <li>• Posaconazole</li> <li>• Erythromycin</li> <li>• Clarithromycin</li> <li>• Telithromycin</li> <li>• HIV protease inhibitors</li> <li>• Boceprevir</li> <li>• Telaprevir</li> <li>• Nefazodone</li> </ul>
<b>Do not exceed 20 mg lovastatin daily with:</b> <ul style="list-style-type: none"> <li>• Gemfibrozil</li> <li>• Other fibrates</li> <li>• Lipid-lowering doses (<math>\geq 1</math> g/day) of niacin</li> <li>• Cyclosporine</li> <li>• Danazol</li> </ul>	<b>Avoid with lovastatin:</b> <ul style="list-style-type: none"> <li>• Cyclosporine</li> <li>• Gemfibrozil</li> </ul>
	<b>Do not exceed 20 mg lovastatin daily with:</b> <ul style="list-style-type: none"> <li>• Danazol</li> <li>• Diltiazem</li> <li>• Verapamil</li> </ul>
<b>Do not exceed 40 mg lovastatin daily with:</b> <ul style="list-style-type: none"> <li>• Amiodarone</li> <li>• Verapamil</li> </ul>	<b>Do not exceed 40 mg lovastatin daily with:</b> <ul style="list-style-type: none"> <li>• Amiodarone</li> </ul>
<b>Avoid large quantities of grapefruit juice (&gt;1 quart daily)</b>	<b>Avoid large quantities of grapefruit juice (&gt;1 quart daily)</b>

VA MedSAFE recommends that facilities continue to report adverse events related to statins or other medications to the VA Adverse Drug Event Reporting System (VA ADERS) as well as to the FDA's Adverse Event Reporting System (AERS-MedWatch). Use of these adverse event-reporting systems helps the VA and FDA observe for trends in adverse events and may help detect

safety signals after a drug is marketed.

### REFERENCES

- FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs. <http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm>. (Accessed 02/28/2012).

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