

MEDICATION

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

SAFETY IN SECONDS

Helping to achieve safe medication use

EFFEXOR XR 150 MG EXTENDED-RELEASE CAPSULES (PFIZER) AND VENLAFAXINE HCL 150 MG EXTENDED-RELEASE CAPSULES (GREENSTONE): RECALL FOR POSSIBLE PRESENCE OF TIKOSYN CAPSULES AND POTENTIAL RISKS OF INADVERTENT USE

A report of the presence of one capsule of Tikosyn (dofetilide) 0.25mg (Figure 1) in a bottle of Effexor XR capsules (Figure 2) resulted in the manufacturers issuing a voluntary recall of:

- one lot of 30-count Effexor XR (venlafaxine HCl) 150 mg extended-release capsules;
- one lot of 90-count Effexor XR (venlafaxine HCl) 150 mg extended-release capsules; and
- one lot of 90-count Greenstone LLC-branded Venlafaxine HCl 150 mg extended-release capsules.

Dofetilide (Tikosyn) is an antiarrhythmic

drug approved for the management of patients with atrial fibrillation/flutter (for the maintenance of normal sinus rhythm in patients with atrial fibrillation/atrial flutter of more than 1 week duration who have been converted to normal sinus rhythm; or conversion of atrial fibrillation and atrial flutter to normal sinus rhythm) whose initiation or reinitiation requires close monitoring (i.e., minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation) to prevent risk of drug-induced life-threatening ventricular arrhythmias. If inadvertently taken,

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Figure 1. The incorrectly contained Tikosyn (dofetilide) is a peach/peach opaque, locking type, hard gelatin capsule.



Figure 2. Effexor XR/Venlafaxine HCl 150mg is an opaque dark orange, locking type, elongated hard gelatin capsule.

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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.

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NEWSWORTHY...

from the pbm

- Effexor and Venlafaxine Recall for Possible Presence of Tikosyn Capsules – 03/10/14 – [National PBM Communication](#)

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from the fda

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INFECTIOUS DISEASE

[FDA approves label changes for antibacterial Doribax \(doripenem\) describing increased risk of death for ventilator patients with pneumonia](#)

3/6/2014

FDA has approved changes to the doripenem (DORIBAX[®]) product label. This change revises the *Warnings and Precautions* section to include a statement indicating that use of doripenem (DORIBAX[®]) is associated with increased mortality when used in the treatment of ventilator-associated pneumonia. The FDA recommends that health care professionals should consider whether the benefits of doripenem (DORIBAX[®]) treatment are likely to exceed its potential risks in patients who develop pneumonia while on ventilators.

This update is based on findings from a prospective, randomized, double-blind, double-dummy, multicenter Phase 3 trial that assessed the efficacy and safety of a fixed 7-day course of doripenem (DORIBAX[®]) (1g, 4-hour infusion, q8h) compared with a fixed 10-day course of imipenem-cilastatin (1g, 1 hour infusion, q8h) for treatment of hospitalized adult patients diagnosed with ventilator-associated pneumonia. Interim analyses of data from over half of the planned subjects showed that in the intent-to-treat population, the doripenem (DORIBAX[®]) arm demonstrated a higher 28-day all-cause mortality (23.0 percent; n=31/135) compared to the imipenem and cilastatin arm (16.7 percent; n=22/132). This finding, coupled with lower clinical cure rates in the doripenem (DORIBAX[®]) arm, led to the premature termination of the trial in 2011.

Doripenem (DORIBAX[®]) is not approved to treat any type of pneumonia. Doripenem (DORIBAX[®]) carries FDA approval for the following indications: treatment of adults with complicated intra-abdominal infections and complicated urinary tract infections including pyelonephritis. The recommended dose of doripenem (DORIBAX[®]) is 500 mg every eight hours intravenously, given over 1 hour, for 5-14 days (depending on indication) in adults. Doses greater than 500 mg every eight hours are not approved. The updated drug label for doripenem (DORIBAX[®]) is available at the following link: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022106s012lbl.pdf.

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2. DORIBAX[®] (doripenem) product package insert. Osaka, Japan: Shionogi & Co. Ltd.; January 2014.
3. FDA Statement on recently terminated clinical trial with Doribax (doripenem). 01/05/2012. <http://www.fda.gov/Drugs/DrugSafety/ucm285883.htm>. (Accessed 03/06/2014)
4. Dear Healthcare Professional Letter. Raritan, NJ: Janssen Pharmaceuticals, Inc.; January 2012. <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM286277.pdf>. (Accessed 03/06/2014)

DIABETES

[FDA Drug Safety Communication: FDA to review heart failure risk with diabetes drug saxagliptin \(marketed as Onglyza and Kombiglyze XR\)](#)

2/11/2014

A recent study published in the New England Journal of Medicine identified a possible association of heart failure with saxagliptin use. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus [SAVOR] – Thrombolysis in Myocardial Infarction [TIMI] 53 study is a randomized, placebo-controlled, phase 4 trial that investigated the efficacy and safety of saxagliptin in diabetic patients at risk for cardiovascular events and suggested an increase in the rate of hospitalization for heart failure, but did not show an increase or decrease in the rate of ischemic events among users of the agent. FDA considers these results as preliminary and will investigate further as well as request clinical trial data from the manufacturer. Additional details are available in the [National PBM Bulletin](#) released last month that addresses saxagliptin and cardiovascular safety.

NEWSWORTHY...

Getting the most from our safety surveillance

TESTOSTERONE THERAPY AND RISK OF ADVERSE CARDIOVASCULAR EVENTS IN MEN

Growing evidence in the medical literature suggests a risk of adverse cardiovascular events associated with the use of testosterone treatment, raising concerns about the potential safety of testosterone therapy. In January 2014, the Food and Drug Administration (FDA) issued a Drug Safety Communication addressing the risk of stroke, heart attack, and death in men undergoing testosterone replacement therapy based on 2 recent studies alluding to an increased cardiac risk. The FDA indicated that their investigation of this potential risk is ongoing, and did not offer definitive conclusions regarding the association of testosterone therapy and adverse cardiovascular events.

One of the studies that prompted FDA to reassess the cardiovascular safety of testosterone therapy took place in the VA. Vigen and colleagues conducted a retrospective analysis evaluating 8709 veterans who underwent coronary angioplasty and had a low serum testosterone (under 300 ng/dL) between 2005 and 2011. The authors wanted to assess the association between testosterone replacement therapy and the composite of all-cause mortality, myocardial infarction (MI), and ischemic stroke while

taking into account any effect of underlying coronary artery disease (CAD).

Results from this observational study suggested a 30 percent increase in risk for stroke, heart attack, and death in the group that received testosterone therapy compared to the group that did not receive any testosterone therapy. Patients were followed for a median of 28 months and 1710 total events occurred in the entire cohort (748 deaths, 443 MIs, and 519 strokes). Of the 8709 patients, 7486 did not receive testosterone therapy and within this group, 681 died, 420 experienced MIs, and 486 had strokes. Among the 1223 (14.0%) that started testosterone therapy (following a median of 531 days post coronary angiography), 67 died, 23 had MIs, and 33 had strokes. The Kaplan-Meier estimated cumulative percentages with events between the no testosterone group and the testosterone group at 1, 2, and 3 years (respectively) after coronary angiography are: 10.1% vs. 11.3% [absolute risk difference 1.3% (95% CI, -7.1% to 9.7%)], 15.4% vs. 18.5% [absolute risk difference 3.1% (95% CI, -4.9% to 11.0%)], and 19.9% vs. 25.7% [absolute risk difference 5.8%

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conduction disturbances that can lead to fatal outcomes may occur in patients with contraindications to dofetilide (Tikosyn) or in at-risk patients who are not appropriately followed. The potential for drug interactions with dofetilide (Tikosyn) and the patient's concomitant medications (including venlafaxine) should also be taken into consideration as certain medications may increase levels of dofetilide (e.g., inhibitors of the CYP3A4 isoenzyme) or have an additive effect of prolonging the QT interval (e.g., other antiarrhythmic agents as well as several other classes of medications) that may increase the risk for life-threatening cardiac arrhythmias including torsades de pointes. Furthermore, based on studies in pregnant animals, dofetilide (Tikosyn) has a potential to increase the risk for adverse fetal outcomes if taken during human pregnancy. Studies of pregnant rats and mice exposed to dofetilide (Tikosyn) during organogenesis showed adverse effects on *in utero* growth and survival, including a variety of fetal structural abnormalities such as cleft palate, adactyly, levocardia, dilation of cerebral ventricles, hydronephrosis, unossified metacarpal, and unossified calcaneum. There are no data on the use of dofetilide (Tikosyn) during human pregnancy. Additionally, there is no

information about levels of dofetilide (Tikosyn) in breast milk and the potential adverse effects of unintended exposure of an infant to dofetilide (Tikosyn) through breast milk.

VA PBM/MedSAFE released a drug safety alert earlier this month to notify VA medical centers of this error in product packaging and to warn health care staff of the unintended consequences of mistakenly taking dofetilide (Tikosyn) instead of Effexor/venlafaxine. The alert also contains instructions for product sequestration and patient notification actions (in the event that a patient received an affected lot) at the local facility level. Additional information is available at the following link: [National PBM Communication](#).

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1. Effexor XR 150 Mg Extended-Release Capsules (Pfizer) and Venlafaxine HCl 150 Mg Extended-Release Capsules (Greenstone): Recall - Possible Presence of Tikosyn Capsules. <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm388352.htm>. (Accessed 03/07/2014)
2. Pfizer Initiates Nationwide Voluntary Recall of Two Lots of Pfizer's Effexor XR® 150 Mg Extended-Release Capsules and One Lot of Greenstone's Venlafaxine HCl 150 Mg Extended-Release Capsules Due to the Possible Presence of Tikosyn® Capsules. <http://press.pfizer.com/press-release/pfizer-initiates-nationwide-voluntary-recall-two-lots-pfizers-effexor-xr-150-mg-extend>. (Accessed 03/12/14)
3. Tikosyn (dofetilide) product package insert. NY, NY: Pfizer Labs; December 2013.

Getting the most from our safety surveillance

TESTOSTERONE THERAPY AND RISK OF ADVERSE CARDIOVASCULAR EVENTS IN MEN

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(95% CI, -1.4% to 13.1%). The authors addressed confounding variables via Cox proportional hazards models using testosterone therapy as a time-varying covariate. Findings showed an association between testosterone treatment and increased risk of adverse outcomes, including all-cause mortality, MI, and ischemic stroke (hazard ratio [HR] 1.29; 95% CI, 1.05-1.58; $p=0.02$). This remained unchanged when adjusted for the presence of CAD (HR 1.29; 95% CI, 1.04-1.58) and even after adding revascularization procedures as another outcome (HR 1.37; 95% CI, 1.21-1.56). Test of interaction revealed no significant difference in the effect size of testosterone therapy between those with and without CAD ($P=0.41$). Different formulations did not influence the risk of adverse outcomes.

An editorial discussed issues raised by the findings in this federal study, specifically the generalizability of the results to a broader population as opposed to the niched veteran cohort characterized by older age and multiple comorbidities. Another critique involved whether or not testosterone was prescribed according to guidelines, which was not addressed in this evaluation. Additionally, limitations in power preclude a conclusion regarding the influence of drug formulation on outcomes. These lingering questions warrant cautious testosterone prescribing and additional investigation.

Although testosterone level may decrease with age, testosterone replacement therapy holds an FDA-approval for use only in men diagnosed with an underlying medical condition that results in severe testosterone deficiency, such as hypogonadism. Uses for “low T syndrome”, anti-aging purposes, or for physical enhancement are not FDA-approved indications. Accepted guidelines for testosterone use recommend evidence of low serum testosterone via morning collection of testosterone on 2 occasions, demonstration of a clinical condition responsible for testosterone deficiency, and appropriate monitoring and follow-up. In light of the mounting evidence signifying a cardiovascular risk, FDA recommends that:

- Providers should consider whether the benefits of FDA-approved testosterone treatment will outweigh the potential risks of treatment.
- Providers should comply with the prescribing information in the product labelling.
- Patients should not discontinue their testosterone treatment without prior discussion with their health care providers.

The VA system has seen a rise in testosterone prescriptions in the past few years. Utilization data shows that use of testosterone products within the VA system has almost tripled in the last six years; and a query of the VA Adverse Drug Event Reporting System (VA ADERS) shows an increase in adverse events reported with testosterone use within that same time frame. More details are available at: <https://vaww.cmopnational.va.gov/cmop/PBM/VAMedSAFE%20Project%20Results%20Select/Forms/AllItems.aspx>.

Providers should continue to report any adverse reactions with the use of testosterone products 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). Additional information can be found in the [National PBM Bulletin](#) that was released last month.

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1. FDA Drug Safety Communication. FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products. <http://www.fda.gov/Drugs/DrugSafety/ucm383904.htm>. Accessed 01/31/2014.
2. Vigen R, O’Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA. 2013; 310(17):1829-1836.
3. Cappola AR. Testosterone therapy and risk of cardiovascular disease in men. JAMA. 2013; 310(17):1805-1806.