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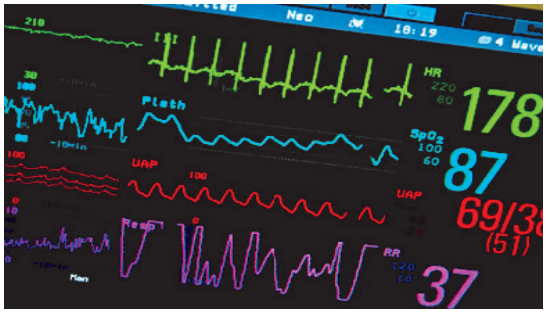
Medication safety in seconds

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

Helping to achieve safe medication use



DROTRECOGIN ALPHA (ACTIVATED) [XIGRIS®] | WORLDWIDE MARKET WITHDRAWAL

On October 25, 2011, Eli Lilly and Company voluntarily withdrew drotrecogin alpha (activated) [Xigris®] from the worldwide market due to lack of a survival benefit for patients with severe sepsis and septic shock.[1] Drotrecogin alfa (activated) [Xigris®], a recombinant human activated protein C (rh-APC), first received approval on November 21, 2001, for mortality reduction in adult patients with severe sepsis at high risk of death. The survival benefit set this agent apart from standard regimens for sepsis that provided anti-infective and supportive measures only. However, benefit remained questionable for patients not meeting the stringent definitions for severe sepsis as defined in the premiere phase III clinical trial documenting its effectiveness (The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis [PROWESS] study).[2]

Since its release into the market, VA has emphasized appropriate use of drotrecogin alfa (activated) [Xigris®] via criteria for use and has tracked safety issues specific to the VA patient population with this agent for over 7 years. Results from a 2002-2003 VA Pharmacy Benefits Management Services (PBM) sponsored drug use evaluation (DUE) based on spontaneous reporting looking at adherence to criteria and adverse drug events (ADEs) were consistent with the FDA's concern of questionable survival benefits outside the stringent definitions used in the phase III trial. These findings identified ahead of the worldwide market withdrawal the uncertainty in the survival benefits to Veterans receiving drotrecogin alfa (activated) [Xigris®], considering that about half of the VA patients that participated in the national DUE experienced mortality during hospitalization.

REFERENCES

1. FDA Drug Safety Communication: Voluntary market withdrawal of Xigris [drotrecogin alfa (activated)] due to failure to show a survival benefit. http://www.fda.gov/Drugs/DrugSafety/ucm277114.htm (Accessed 10/25/2011).
2. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344: 699-709.

NEWS YOU CAN USE

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

- Lexiscan® (Regadenoson) Update: New Safety Labeling Changes Approved By FDA - National PBM Communication – 11-15-2011
- Target Dose of Angiotensin II Receptor Antagonists in Patients with Heart Failure - National PBM Communication – 10-31-2011

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

NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

Trilipix - Review update of Trilipix (fenofibric acid) and the ACCORD Lipid Trial
11/09/2011
Adding Trilipix® (fenofibric acid) may not lower risk of heart attack or stroke, based on data from the **A**ction to **C**ontrol **C**ardiovascular **R**isk in **D**iabetes (ACCORD) Lipid trial, which evaluated efficacy and safety of fenofibrate plus simvastatin combination therapy versus simvastatin alone in patients with type 2 diabetes mellitus. Results from this study showed a non-significant 8% relative risk reduction in the primary outcome of major adverse cardiovascular (CV) events (hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.79-1.08; p=0.32) when comparing fenofibrate plus simvastatin combination therapy to simvastatin plus placebo. Updated labeling now includes information from this trial. Based on these results and other clinical trials of similar drugs, FDA requires additional studies from the manufacturer of Trilipix® to evaluate the CV effects of Trilipix® in patients at high risk for CV disease already taking statins.

Avandia (rosiglitazone) - Reminder to healthcare providers and patients to enroll in the Avandia-Rosiglitazone Medicines Access Program
11/04/2011 **(***UPDATE FROM 05/18/2011***)**
After November 18, 2011, retail pharmacies will no longer carry rosiglitazone medicines (Avandia®, Avandamet®, and Avandaryl®). Access to rosiglitazone-containing medications will occur via mail order through certified pharmacies participating in the Avandia-Rosiglitazone Medicines Access Program. Healthcare providers must enroll in the program in order to prescribe rosiglitazone medicines on an outpatient basis. Healthcare providers must also enroll eligible patients for rosiglitazone initiation or maintenance therapy.

TNF Blockers - UPDATE on Tumor Necrosis Factor (TNF) blockers and risk for pediatric malignancy
11/03/2011 **(***UPDATE FROM 04/14/2011***)**
FDA reported malignancy associated with Tumor Necrosis Factor (TNF) blockers in June 2008, August 2009, and April 2011. As part of its ongoing safety review of TNF blockers and malignancy in children, adolescents, and young adults (≤30 years of age), FDA now requires manufacturers to perform enhanced safety surveillance for TNF blockers including:

- Detailed reports of malignancy cases and respective follow-up submitted as expedited reports to FDA;
- Annual summaries and assessments of malignancies and TNF blocker utilization data.

ADHD - Safety Review Update of Medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in children and young adults
11/01/2011
Increases in blood pressure and heart rate observed in patients treated with sympathomimetics (e.g., methylphenidate and amphetamine) and with atomoxetine, coupled with spontaneous postmarketing reports of serious cardiovascular (CV) events associated with use of ADHD drugs, has lead FDA (in partnership with AHRQ) to sponsor three separate but related observational studies evaluating serious CV events with drugs used for ADHD. Adverse CV events examined include stroke, heart attack (myocardial infarction or MI), and sudden cardiac death. The medications studied include stimulants (amphetamine products and methylphenidate), atomoxetine, and pemoline (no longer marketed). The first study did not find an association between use of ADHD medications and CV events (7 serious CV events [4 strokes and 3 sudden cardiac deaths]) in current ADHD drug users (1,200,438 children and young adults [aged 2-24 years]). Results from the other two studies (performed in adults) remain pending. FDA continues to recommend that healthcare professionals prescribe these medications according to the professional prescribing label.

Drospirenone - Updated information about the FDA-funded study on risk of blood clots in women taking birth control pills containing drospirenone
10/27/2011 **(*** UPDATE FROM 09/26/2011***)**
The final report of the FDA-funded study that evaluated the risk of blood clots in users of several different hormonal contraceptives (including drospirenone-containing birth control products) will be presented and discussed at the joint meeting of the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on December 8, 2011.

Xigris [drotrecogin alfa (activated)] - Voluntary market withdrawal of Xigris [drotrecogin alfa (activated)] due to failure to show a survival benefit
10/25/2011
On October 25, 2011, Eli Lilly and Company voluntarily withdrew drotrecogin alpha (activated) [Xigris®] from the worldwide market due to lack of a survival benefit for patients with severe sepsis and septic shock. Preliminary analyses done by the manufacturer and submitted to the FDA showed a 28-day all cause mortality rate of 26.4% (223/846) in Xigris-treated patients compared to 24.2% (202/834) in placebo-treated patients, for a relative risk of 1.09; 95% CI (0.92, 1.28), and P-value = 0.31 (not statistically significant). Recommendations include:

- *Xigris treatment should not be started in new patients.*
- *Xigris treatment should be stopped in patients being treated with Xigris.*
- *All remaining Xigris product should be returned to the supplier from whom it was purchased.*

Chantix (varenicline) - Safety review update of Chantix (varenicline) and risk of neuropsychiatric adverse events
10/24/2011
FDA sponsored two epidemiological studies – a Department of Veterans Affairs' (VA) Center for Medication Safety (VAMedSAFE) study and a Department of Defense (DoD) study. Both studies evaluated the risk of neuropsychiatric hospitalizations associated with the smoking cessation drug varenicline (Chantix®) , and each resulted in no difference between varenicline (Chantix®) and nicotine replacement therapy (NRT; e.g., NicoDerm patches). Due to study design limitations, the results do not preclude the increased risk of ANY neuropsychiatric event with varenicline (Chantix®). The manufacturer of varenicline (Chantix®), Pfizer, continues to assess neuropsychiatric adverse events via a large safety clinical trial with results expected in 2017.

Linezolid (Zyvox) - Updated information about the drug interaction between linezolid (Zyvox) and serotonergic psychiatric medications
10/20/2011 **(*** UPDATE FROM 07/26/2011***)**
Serotonergic medications may cause serotonin syndrome to different degrees when taken with linezolid. Cases of serotonin syndrome with linezolid reported to the FDA's Adverse Event Reporting System (AERS) occurred in patients taking specific serotonergic medications including: paroxetine (Paxil®, Paxil CR®), fluvoxamine (Luvox®, Luvox CR®), fluoxetine (Prozac®, Symbyax®), sertraline (Zoloft®), citalopram (Celexa®), escitalopram (Lexapro®), vilazodone (Viibryd®), venlafaxine (Effexor®, Effexor XR®), desvenlafaxine (Pristiq®), and duloxetine (Cymbalta®).

NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

(continued from page 2)

Methylene Blue - Updated information about the drug interaction between methylene blue (methylthioninium chloride) and serotonergic psychiatric medications

10/20/2011 **(*** UPDATE FROM 07/26/2011***)**

Most reports of serotonin syndrome in patients given serotonergic medications concomitantly with methylene blue occurred in the setting of parathyroid surgery, where methylene blue was administered intravenously (doses ranged from 1 mg/kg to 8 mg/kg) as a visualizing agent. The risk of serotonin syndrome remains unknown in patients on serotonergic agents who also take methylene blue orally or by local tissue injection, as well as at intravenous doses lower than 1 mg/kg. Serotonergic medications may cause serotonin syndrome to different degrees when taken with methylene blue. Cases of serotonin syndrome with methylene blue reported to the FDA's Adverse Event Reporting System (AERS) occurred in patients taking specific serotonergic medications including: paroxetine (Paxil®, Paxil CR®), fluvoxamine (Luvox®, Luvox CR®), fluoxetine (Prozac®, Symbyax®), sertraline (Zoloft®), citalopram (Celexa®), escitalopram (Lexapro®), vilazodone (Viibryd®), venlafaxine (Effexor®, Effexor XR®), desvenlafaxine (Pristiq®), duloxetine (Cymbalta®), and clomipramine (Anafranil®).

Sprycel - Sprycel (dasatinib) and risk of pulmonary arterial hypertension

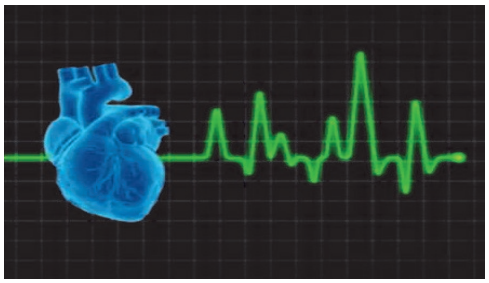
10/11/2011

Sprycel® (dasatinib) was initially approved in June 2006 for leukemia. Since that time, Bristol-Myers Squibb received reports of cases of pulmonary arterial hypertension (PAH) in their global pharmacovigilance database.

- Twelve cases of PAH were confirmed by right heart catheterization.
- No fatalities from the condition have been reported.
- Symptoms of PAH include dyspnea, fatigue, hypoxia, and fluid retention.
- PAH may occur anytime after initiation, up to more than one year of treatment.
- PAH diagnoses may be confounded by concomitant medications or co-morbidities.
- In some cases, discontinuation of Sprycel® lead to clinical and hemodynamic improvements.

Healthcare professionals should evaluate patients for signs and symptoms of underlying cardiopulmonary disease when considering Sprycel® treatment. Permanently discontinue Sprycel® upon confirmed PAH.

Getting the most from our safety surveillance



PRASUGREL (EFFIENT®) MONITORING | INAPPROPRIATE USE AND BLEEDING EVENTS

Prasugrel, a potent thienopyridine antiplatelet agent, gained approval for use in patients with acute coronary syndromes (ACS) and undergoing percutaneous coronary intervention (PCI). However, safety concerns exist with the use of this agent. Compared with clopidogrel, prasugrel has a higher risk of bleeding. Further, prasugrel product labeling contraindicates use in patients with a history of transient ischemic attack (TIA) or stroke due to a higher risk of stroke observed in these patients during clinical trials. [1]

The VA Center for Medication Safety (VA MedSAFE) quarterly monitors prasugrel for bleeding events as well as inappropriate use in patients with the aforementioned contraindication. The most recent review covered the time period from 08/01/2009 through 06/30/2011. Overall, rates of potentially inappropriate use of prasugrel and bleeding events remain low and fairly stable compared with previous reports. Results indicate that out of a total of 1937 patients (new users and switchers from clopidogrel) who received a prescription for prasugrel:

- Some had a contraindication (history of TIA/stroke).
    - A total of 37 patients (14 new users [1.24%] and 23 switchers [2.84%]) were identified using a stringent and validated definition of prior inpatient diagnosis of TIA or stroke.
    - An additional 15 patients (7 new patients [0.62%] and 8 switchers [0.99%]) were identified when considering outpatient diagnoses of TIA or stroke in efforts to capture additional patients who may have a contraindication to prasugrel as diagnosed outside of VA.
- 13.21% of new users and 13.42% of switchers were identified as being 75 years of age and older, which can increase risk of serious bleeding complications.
- 57 patients experienced new bleeding (31 new users [2.75%] and 26 switchers [3.2%]).
- 72 patients had a history of bleeding (37 new users [3.28%] and 35 switchers [3.21%]).

As a comparison, additional VAMedSAFE data analysis found similar bleeding rates with clopidogrel use as observed with prasugrel use (clopidogrel: 2.95% new bleeds and 3.07% history of bleed).

Based on these data, and as recommended by the Medical Advisory Panel (MAP) and the VISN Pharmacist Executives (VPE) group, VA MedSAFE has identified patients with a potential contraindication that may have received a prasugrel prescription for chart review to determine appropriateness of continued prasugrel therapy. This list was forwarded to VPEs in September 2011 for local adjudication and follow-up.

REFERENCES

1. Effient® (prasurgel) [package insert]. Indianapolis, IN: Eli Lilly and Company; September 2011.

Contributed by: Lisa Longo, Pharm.D., B.C.P.S.