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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

FDA AND CDC IDENTIFY SOURCE OF MULTISTATE BURKHOLDERIA CEPACIA INFECTION OUTBREAKS ASSOCIATED WITH CONTAMINATED ORAL LIQUID DOCUSATE PRODUCTS

Submitted by Jessica Zacher, Pharm. D., PGY-2 Medication Use Safety Pharmacy Resident

Last June, PBM/MedSAFE issued a National PBM Patient Level Recall Communication addressing contaminated oral liquid docusate products. At that time, it was not clear which products and manufacturers were impacted and CDC recommended the sequestration of all liquid docusate products because of cases of *Burkholderia cepacia* (*B. cepacia*) infections in one state. After further investigation, the FDA has recently found that the previously reported contamination of oral liquid docusate sodium with *B. cepacia* is associated with multiple lots manufactured by PharmaTech in Davie, Florida. It was also determined that the water system utilized in the Davie, FL manufacturing facility is contaminated with *B. cepacia*. The affected products were all manufactured by PharmaTech, and distributed by the following firms: Rugby, Major, Bayshore, Metron, Centurion, and Virtus. Samples that were inspected from other oral liquid docusate sodium manufacturers did not contain the bacteria. Based on laboratory evidence from CDC and FDA, PharmaTech appears to be the source of the *B. cepacia* outbreak in oral liquid docusate products, and the active pharmaceutical ingredient used to manufacture oral liquid docusate does not appear to be a source of the outbreak. The published update concludes that health care professionals may use oral liquid docusate products manufactured by firms other than PharmaTech, and reminds manufacturers of the importance of robust manufacturing with testing of liquid products to assure that they are not contaminated. Patients and health care professionals should continue to report adverse events related to *B. cepacia* in oral liquid docusate products to FDA's MedWatch Adverse Event Reporting Program.

REFERENCE:

FDA Updates on Multistate Outbreak of Burkholderia cepacia Infections. http://www.fda.gov/Drugs/DrugSafety/ucm511527.htm . Accessed 10/13/2016.

NEWSWORTHY... from the pbm

- Liquid Products Recall (PharmaTech) Due to Potential Risk of Product Contamination – 10/12/16 - National PBM Patient Level Recall Communication
- GlucaGen® HypoKit® (Novo Nordisk Inc.) Recall Due to Needle Detachment from Syringe – 09/14/16 - National PBM Patient Level Recall Communication
- Eye Wash/Eye Irrigating Soutions Recall Due to Microbial Contamination - 09/09/16 - National PBM Patient Level Recall Communication

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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 fda

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INFECTIOUS DISEASES

FDA warns about the risk of hepatitis B reactivation in some patients treated with direct-acting antivirals for hepatitis C

10/4/2016

Submitted by Jessica Zacher, Pharm.D., PGY-2 Medication Use Safety Pharmacy Resident

The FDA will require *boxed warnings* to be added to the drug labels of certain direct-acting antiviral medications (DAAs, see list below) used to treat hepatitis C virus (HCV). Findings from 24 cases reported to the FDA Adverse Event Reporting System (FAERS) and from published literature showed:

- An increased risk of reactivating hepatitis B virus (HBV) infection in patients treated with DAA medications for HCV infection.
- Fulminant hepatitis, hepatic decompensation (n=3), and death (n=2) has occurred in cases where HBV was reactivated.

The current mechanism of hepatitis B reactivation is not known. HBV reactivation was not previously documented as an adverse event during clinical trials for the DAAs because patients with HBV co-infection were excluded . Reactivation is characterized by a sharp increase in HBV replication, which can be seen via laboratory testing as:

- A sharp increase in the serum HBV DNA level; or
- Detection of the HbsAg in a patient who was previously HbsAg negative and anti-HB-c positive.

Of the 24 cases reported between November 2013 to July 2016:

- HBV reactivation developed between 4-8 weeks (52 days on average) after HCV treatment initiation.
- Only 12 of these 24 cases had reports of the patients receiving treatment for HBV.
  - In at least 5 of those 12 cases, treatment was delayed, of which one patient died and another required transplantation.

In light of these findings, FDA recommends that *health care professionals:*

- Prior to initiating DAA treatment, screen all patients for:
  - Evidence of active HBV or a history of HBV.
    - Test for hepatitis B surface antigen (HbsAg) and hepatitis B core antibody (anti-HB-c).
    - In patients with serologic evidence of HBV infection, measure baseline HBV DNA level prior to initiating a DAA.
  - Liver problems other than HCV infection, such as cirrhosis.
  - Human Immunodeficiency Virus (HIV) infection.
- Monitor patients for evidence of current or prior HBV infection via clinical and laboratory indicators of HBV flare-ups or reactivation throughout treatment with DAAs, and during follow-up after treatment has ended.
  - Laboratory indicators: HbsAg, HBV DNA, serum aminotransferase levels, bilirubin.
- Consult with hepatology or infectious disease specialists for advice on the monitoring and consideration of HBV antiviral treatment in HCV/HBV co-infected patients.
- Counsel patients to contact a health care professional if signs of serious liver injury, including fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light colored stools develop.

List of Direct-Acting Antivirals (DAAs)

Brand name	Active ingredient(s)	Manufacturer
Daklinza	daclatasvir	Bristol-Myers Squibb
Epclusa	sofosbuvir/velpatasvir	Gilead Sciences
Harvoni	ledipasvir/sofosbuvir	Gilead Sciences
Olysio	simeprevir	Janssen
Sovaldi	sofosbuvir	Gilead Sciences
Technivie	ombitasvir/paritaprevir/ritonavir	Abbvie
Viekira Pak	dasabuvir/ombitasvir/paritaprevir/ritonavir	Abbvie
Viekira Pak XR	dasabuvir/ombitasvir/paritaprevir/ritonavir	Abbvie
Zepatier	elbasvir/grazoprevir	Merck Sharp Dohme

*The DAA, Victrelis (boceprevir) and Incivek (telaprevir) are not included in the list as they are used in combination with interferon and are no longer available in the United States.

REFERENCE:

FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C. http://www.fda.gov/Drugs/DrugSafety/ucm522932.htm . (Accessed October 6, 2016).

Getting the most from our safety surveillance

PRESCRIBING INFORMATION FOR CONSIDERATION—A LIST OF MEDICATIONS CARRYING A SUICIDALITY WARNING

Submitted by Anthony Au, Pharm.D., BCPS

The intent of the Warnings and Precautions section of drug labeling is to identify and describe adverse reaction and/or safety issues that would impact the prescribing decision of a particular medication.[1] In a previous paper, we compiled a list of prescription medications with a warning label for suicidal ideation or behavior and described the utilization pattern in the Department of Veterans Affairs.[2] Below, we have updated the list of medications that carries a suicidality warning as new prescription medications have been approved by the Food and Drug Administration (FDA) since the original publication in 2012.

The compilation of this medication list was conducted via an electronic search through individual prescribing information drug labels. The information source used for this search was the DailyMed repository.[3] DailyMed is a website comprised of the most up-to-date labeling information submitted to the FDA. The use of DailyMed allowed for keyword search on individual drug labels. The keywords used for this search include: suicidality, suicidal behavior and suicidal ideation. The search was conducted in May of 2016.

REFERENCES:

1. Guidance for the Industry: Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products - Content and Format Accessed 14 Oct 2016: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf
2. Lavigne, J.E., Au, A., Jiang, R. et al. Utilization of prescription drugs with warnings of suicidal thoughts and behaviours in the USA and the US Department of Veterans Affairs, 2009. J Pharm HSR. 2012;3:157–163.
3. DailyMed Website Accessed 07 May 2016: https://dailymed.nlm.nih.gov/dailymed/advanced-search.cfm ■

Figure 1. List of medications carrying a suicidality warning . *(*) Denotes newly added medications.*

Acamprosate	Efavirenz/emtricitabine/tenofovir	Meprobamate	Ribavirin
Alprazolam	Emtricitabine/Rilpivirine/Tenofovir*	Methosuximide	Rilpivirine*
Amantadine	Escitalopram	Metoclopramide	Risperidone
Amitriptyline	Eslicarbazepine*	Milnacipran	Roflumilast*
Amobarbital	Estazolam	Mirtazapine	Rufinamide
Amoxapine	Eszopiclone	Modafinil	Secobarbital
Apremilast*	Ethosuximide	Montelukast	Selegiline
Aripiprazole	Ethotoin	Moxifloxacin	Sertraline
Armodafinil	Ezogabine*	Mysoline	Sibutramine
Asenapine	Felbamate	Naltrexone	Sodium Oxybate
Atomoxetine	Fluoxetine	Nefazodone	Suvorexant*
Belimumab*	Fluphenazine	Nortriptyline	Temazepam
Brexipiprazole*	Flurazepam	Ofloxacin	Tetrabenazine
Brivaracetem	Fluvoxamine	Olanzapine	Tiagabine
Bupropion	Gabapentin	Olanzapine/fluoxetine	Topiramate
Butabarbital	Gemifloxacin	Oxacarbamazapine	Tramadol
Carbamazepine	Iloperidone	Paliperidone	Tranylcypromine
Carbidopa	Imipramine	Paroxetine	Trazodone
Carbidopa/levidopa	Interferon alfa-2B	Peginterferon Alfa-2A	Triazolam
Carbidopa/levidopa/entacapone	Interferon beta-1A	Peginterferon Alfa-2B	Trimethadione
Chlordiazepoxide	Interferon beta-1B	Pentobarbital	Trimipramine
Chlordiazepoxide/amitriptyline	Isocarboxazid	Perampanel*	Valproate
Ciprofloxacin	Isotretinoin	Perphenazine	Valproic acid
Citalopram	Lacosamide	Perphenazine/amitriptyline HCl	Varenicline
Clobazem*	Lamotrigine	Phenelzine	Venlafaxine
Clomipramine	Levetiracetam	Phenobarbital	Vigabatrin
Clonazepam	Levofloxacin	Phenytoin	Vilazadone*
Clorazepate	Levomilnacipran*	Pregabalin	Vortioxetine*
Clozapine	Liraglutide*	Primidone	Zafilukast
Desipramine	Lorazepam	Propoxyphene	Zaleplon
Desvenlafaxine	Lorcaserin*	Propoxyphene/acetaminophen	Ziconotide
Diazepam	Lurasidone*	Protriptyline	Zileuton
Divalproex	Maprotiline	Quazepam	Ziprasidone
Doxepin	Mefloquine	Quetiapine	Zolpidem
Duloxetine	Mephenytoin	Ramelteon	Zonisamide
Efavirenz	Mephobarbital	Reserpine	