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:

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 Solutions Recall Due to Microbial Contamination - 09/09/16 - National PBM Patient Level Recall Communication

(continued on page 2)
FDA warns about the risk of hepatitis B reactivation in some patients treated with direct-acting antivirals for hepatitis C.

10/4/2016

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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)

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Active ingredient(s)</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daklinza</td>
<td>daclatasvir</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Epclusa</td>
<td>sofosbuvir/velpatasvir</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Harvoni</td>
<td>ledipasvir/sofosbuvir</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Olysio</td>
<td>simeprevir</td>
<td>Janssen</td>
</tr>
<tr>
<td>Sovaldi</td>
<td>sofosbuvir</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Technivie</td>
<td>ombitasvir/paritaprevir/ritonavir</td>
<td>Abbvie</td>
</tr>
<tr>
<td>Viekira Pak</td>
<td>dasabuvir/ombitasvir/paritaprevir/ritonavir</td>
<td>Abbvie</td>
</tr>
<tr>
<td>Viekira Pak XR</td>
<td>dasabuvir/ombitasvir/paritaprevir/ritonavir</td>
<td>Abbvie</td>
</tr>
<tr>
<td>Zepatier</td>
<td>elbasvir/grazoprevir</td>
<td>Merck Sharp Dohme</td>
</tr>
</tbody>
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*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:
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. 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. 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. 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:

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

Acamprosate  Efavirenz/Emtricitabine/Tenofovir  Meprobamate  Ribavirin
Alprazolam  Emtricitabine/Rilpivirine/Tenofovir*  Methoxuximide  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*  Myocilone  Sibutramine
Asenapine  Felbamate  Naltrexone  Sodium Oxybate
Atomoxetine  Fluoxetine  Nefazodone  Suvorexant*
Belinumab*  Fluphenazine  Nortriptyline  Temazepam
Brexpiprazole*  Flurazepam  Ofloxacin  Tetrabenazine
Brivaracetam  Fluvoxamine  Olanzapine  Tiagabine
Bupropion  Gabapentin  Olanzapine/Fluoxetine  Topiramate
Butabarbital  Gemifloxacin  Oxacarbamazine  Tramadol
Carbamazepine  Iloperidone  Paliperidone  Tranylcypromine
Carbidopa  Imipramine  Paroxetine  Trazodone
Carbidopa/Levodopa  Interferon alfa-2B  Peginterferon Alfa-2A  Triazolam
Carbidopa/Levodopa/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  Peripherazine/amitriptyline HCI  Varenicline
Clobazem*  Lamotrigine  Phenelzine  Venlafaxine
Clomipramine  Levetiracetam  Phenoxybarbital  Vigabatrin
Clonazepam  Levofloxacin  Phenytoin  Vilazodone*
Clorazepate  Levomilnacipran*  Pregabalin  Vortioxetine*
Clozapine  Liraglutide*  Pramidone  Zafirlukast
Desipramine  Lorazepam  Proproxynaphene  Zaleplon
Desvenlafaxine  Lorcaserin*  Propoxyphene/acetaminophen  Ziconotide
Diazepam  Lurasidone*  Protriptyline  Zileuton
Divalproex  Mefloquine  Quazepam  Ziprasidone
Doxepin  Mephenytoin  Quetiapine  Zolpidem
Duloxetine  Methotrexate  Ramelteon  Zonisamide
Efavirenz  Mepobarbital  Reserpine