



NATIONAL PBM BULLETIN

MARCH 14, 2017

DEPARTMENT OF VETERANS AFFAIRS
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
VISN PHARMACIST EXECUTIVES (VPEs), AND THE CENTER FOR MEDICATION SAFETY (VA MedSAFE)

DIRECT-ACTING ANTIVIRAL (DAA) AGENTS FOR HCV TREATMENT AND LIVER SAFETY ISSUES

I. ISSUE

A recent Institute for Safe Medication Practices (ISMP) QuarterWatch report addresses serious hepatic adverse events in patients receiving direct-acting antiviral (DAA) medications for treatment of hepatitis C virus (HCV). While this Bulletin points out reports of hepatotoxicity associated with DAAs, these agents have been shown to be highly effective in treating HCV infection and, when used appropriately, are safe and easy to take.

II. BACKGROUND

ISMP conducted a review of hepatic safety issues related to DAA use for HCV treatment after an FDA analysis from October 2016 described an increased risk of reactivating hepatitis B virus (HBV) infection in a small group of patients (n=24) treated with DAA medications for HCV infection, which resulted in fulminant hepatitis, hepatic decompensation (n=3), and death (n=2). FDA's findings led to the addition of a boxed warning to the labeling of the newer antivirals, with recommendations for providers to screen and monitor for HBV in all patients taking the drugs for HCV. FDA's review was addressed in the [Issue 9; Volume 6; October 2016](#) edition of the medication safety newsletter published by the VA Pharmacy Benefits Management Services (PBM) and Center for Medication Safety (MedSAFE). To follow up on these findings, ISMP further investigated the safety issues related to DAA treatment.

III. DISCUSSION

ISMP FINDINGS

ISMP searched the most recent 12 months (ending June 30, 2016) of data from the FDA Adverse Event Reporting System (FAERS) for liver failure cases associated with DAAs and identified:

- 524 reported cases of liver failure.
 - 55% occurred in males; the median age was 61 years.
 - 31.5% had an outcome of death at the time the report was submitted.
 - 73.7% were reported outside of the US.
 - Table 1 (page 3) shows the types of liver failure identified in reports reviewed by ISMP.
 - Table 2 (page 3) shows the primary and secondary suspect drugs associated with the reports of liver failure above.
- 1,058 reports of severe liver injury that did not progress to liver failure.
 - This refers to “Drug related hepatic disorders – severe events only”. However, no information was provided as to the other drugs the patient may have been taking or what the disorder may have been.

LIMITATIONS OF ISMP'S REVIEW

This report has several important and notable limitations. No information was reported on patient stage of disease, particularly whether or not these events occurred in patients with known cirrhosis, decompensated cirrhosis, or those who may have been pre- or post-transplant. Additionally, the HBV status of these patients is unknown. As many of the terms used in the search are commonly present in HCV infected patients with advanced disease, particularly those with



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decompensated cirrhosis, it cannot be determined if these events would have occurred as part of the natural progression of HCV disease itself in the absence of HCV antiviral treatment.

MONITORING EFFORTS WITHIN VA

VA continues to monitor adverse events for the DAAs at the national level through the VA Adverse Drug Event Reporting System (VA ADERS). VA also conducts active surveillance system-wide through Rapid Cycle Evaluations to assess potential adverse event signals that may arise with these agents. Both passive surveillance and active surveillance results are presented to the Hepatitis C Subject Matter Experts and Medical Advisory Panel members on an ongoing basis. National surveillance data within the VA to date shows negligible signal for increased hepatic decompensation associated with DAA use and a low signal for HBV reactivation with only 9 of 62,240 veterans treated with DAAs identified as exhibiting evidence of HBV reactivation; of these, only 3 had an associated hepatitis flare. A HBV reactivation MUET is being developed to monitor patients, and assure that those with identified risks are tested for HBV and assessed immediately, in alignment with FDA guidance. This MUET is scheduled for implementation in early Spring 2017. VA Guidance on HBV is available at: <http://vaww.hepatitis.va.gov/pdf/hbv-recommendations-hcv-daa-treatment.pdf>.

IV. RECOMMENDATIONS

Providers should continue to monitor patients receiving DAAs for evidence of unexpected consequences and report any adverse reactions with the use of DAA products for treatment of HCV infection 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).

Moreover, FDA previously communicated the following recommendations (also stated in the [Issue 9; Volume 6; October 2016](#) of PBM/MedSAFE's Medication Safety in Seconds newsletter) as their analysis of DAA use in HCV treatment attributed the cause of liver complications to reactivation of HBV infection:

- Prior to initiating DAA treatment, screen all patients for:
 - Evidence of active HBV (i.e., presence of HbsAg) or a history of HBV (i.e., presence of anti-HB-c).
 - 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

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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 develop, including fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light colored stools.

V. REFERENCES

1. Institute for Safe Medication Practices (ISMP). New Safety Issues for Hepatitis C Antivirals. *ISMP Quarter Watch: Monitoring FDA Medwatch Reports* January 25, 2017; 2016 Q2: 11-15.
2. 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).

Table 1. Types of liver failure identified in reports reviewed by ISMP.

Preferred Term	Number of Occurrences Reported* (Note: A report may contain multiple terms.)
Hepatic Failure	275
Hepatic Encephalopathy	214
Liver Transplant	55
Acute Hepatic Failure	27
Hepatorenal Failure	6
Acute on Chronic Liver Failure	4
Coma Hepatic	2
Subacute Hepatic Failure	1

*Percent of unique cases N=524.

Table 2. Primary (PS) and secondary (SS) suspect drugs associated with reports of liver failure from ISMP review above.

Brand name	Active ingredient(s)	PS	SS	Total	Percent (%)
Daklinza	daclatasvir	74	25	99	18.9
Harvoni	ledipasvir/sofosbuvir	116	5	121	23.1
Olysio	simeprevir	16	21	37	7.1
Sovaldi	sofosbuvir	91	80	171	32.6
Viekira Pak**	dasabuvir/ombitasvir/paritaprevir/ritonavir	120	61	181	34.5
Zepatier	elbasvir/grazoprevir	1	0	1	0.2

**Includes Technivie, Viekira XR.

ACTIONS

- **Facility Director (or physician designee):** Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers and health care staff (e.g., **primary care providers, infectious disease specialists, GI/hepatology, including contract providers, etc.**). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).