



U.S. Food and Drug Administration
Protecting and Promoting Your Health

Drug Safety Communications

FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C

Safety Announcement

[10-04-2016] The U.S. Food and Drug Administration (FDA) is warning about the risk of hepatitis B virus (HBV) becoming an active infection again in any patient who has a current or previous infection with HBV and is treated with certain direct-acting antiviral (DAA) medicines for hepatitis C virus. In a few cases, HBV reactivation in patients treated with DAA medicines resulted in serious liver problems or death.

As a result, we are requiring a *Boxed Warning*, our most prominent warning, about the risk of HBV reactivation to be added to the drug labels of these DAAs directing health care professionals to screen and monitor for HBV in all patients receiving DAA treatment. This warning will also be included in the patient information leaflet or [Medication Guides](#) for these medicines.

Direct-acting antiviral medicines are used to treat chronic hepatitis C virus (HCV) infection, an infection that can last a lifetime. These medicines reduce the amount of HCV in the body by preventing HCV from multiplying, and in most cases, they cure HCV. Without treatment, HCV can lead to serious liver problems including cirrhosis, liver cancer, and death (see List of Direct-Acting Antivirals).

Health care professionals should screen all patients for evidence of current or prior HBV infection before starting treatment with DAAs, and monitor patients using blood tests for HBV flare-ups or reactivation during treatment and post-treatment follow-up. It is currently unknown why the reactivation occurs.

Patients should tell your health care professional if you have a history of hepatitis B infection or other liver problems before being treated for hepatitis C. Do not stop taking your DAA medicine without first talking to your health care professional. Stopping treatment early could result in your virus becoming less responsive to certain hepatitis C medicines. Read the patient information leaflet or [Medication Guide](#) that comes with each new prescription because the information may have changed. Contact your health care professional immediately if you develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools, as these may be signs of serious liver problems.

We identified 24 cases of HBV reactivation reported to FDA¹ and from the published literature in HCV/HBV co-infected patients treated with DAAs during the 31 months from November 22, 2013 to July 18, 2016.²⁻⁷ This number includes only cases submitted to FDA, so there are likely additional cases about which we are unaware. Of the cases reported, two patients died and one

required a liver transplant. HBV reactivation was not reported as an adverse event in the clinical trials submitted for the DAA approvals because patients with HBV co-infection were excluded from the trials. The trials excluded these patients in order to specifically evaluate the safety of DAAs, including their effects on the liver, in patients infected with only HCV and without the presence of another virus which affects the liver (see Data Summary).

We urge health care professionals and patients to report side effects involving DAAs and other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

List of Direct-Acting Antivirals (DAAs)*

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

* DAA regimens not requiring use in combination with interferon. The DAA medicines, 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.

Facts about Direct-Acting Antivirals (DAAs)

- Direct-acting antivirals (DAAs) are a class of prescription medicines that are FDA-approved to treat adults with hepatitis C virus (HCV) infection. These medicines are available as single-ingredient products and also in combination with other HCV medicines (see List of Direct-Acting Antivirals).
- DAAs reduce the amount of HCV in the body by preventing the virus from multiplying and, in most cases, cure HCV.
- Before starting DAA treatment, patients should tell their health care professionals if they:
 - Have current hepatitis B infection or have had hepatitis B infection in the past
 - Have liver problems other than HCV infection, such as cirrhosis
 - Have human immunodeficiency virus (HIV) infection
- Common side effects of DAAs depend on the specific medicines but can include tiredness, headache, and nausea.

Additional Information for Patients and Caregivers

- If you have had hepatitis B or are a carrier of hepatitis B virus (HBV), taking certain medicines called direct-acting antivirals (DAAs) to treat hepatitis C virus (HCV) infection could cause the HBV to become an active infection again. HBV reactivation may cause serious liver problems, including liver failure and death.
- Before taking DAA treatment, tell your health care professional if you have a history of hepatitis B infection or other liver problems.
- If you have had HBV, your health care professional should monitor you with blood tests to see if HBV infection becomes active while you are taking DAAs and for months after you stop taking DAAs.
- Talk to your health care professional if you have any questions or concerns about your HCV treatment.
- Contact your health care professional immediately if you develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools, as these may be signs of serious liver problems.
- Carefully read the patient information leaflet or [Medication Guide](#) that comes with your DAA drug prescriptions.
- Report any side effects from DAAs or other medicines to your health care professional and the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

Additional Information for Health Care Professionals

- Hepatitis B virus (HBV) reactivation has occurred in patients co-infected with hepatitis C virus (HCV) while undergoing treatment with DAAs for HCV infection. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. This risk has been observed with DAAs used without interferon to treat HCV infection.
- HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of hepatitis B surface antigen (HBsAg) in a person who was previously HBsAg negative and hepatitis B core antibody (anti-HBc) positive. Reactivation of HBV replication is often followed by hepatitis, i.e., an increase in transaminase levels and, in severe cases, an increase in bilirubin levels, hepatic failure, and death.
- The mechanism through which HBV reactivation occurs is currently unknown.
- Cases of HBV reactivation have been reported in HCV patients treated with DAAs who are hepatitis B surface antigen (HBsAg) positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive), and were not receiving HBV antiviral treatment.
- To decrease the risk of HBV reactivation in patients co-infected with HBV and HCV, health care professionals should:
 - Screen all patients for evidence of current or prior HBV infection before initiating treatment with DAAs by measuring HBsAg and anti-HBc. In patients with serologic evidence of HBV infection, measure baseline HBV DNA prior to DAA treatment.

- Monitor patients who show evidence of current or prior HBV infection for clinical and laboratory signs (i.e., HBsAg, HBV DNA, serum aminotransferase levels, bilirubin) of hepatitis flare or HBV reactivation during DAA treatment and post-treatment follow-up.
- Consult a physician with expertise in managing hepatitis B regarding the monitoring and consideration for HBV antiviral treatment in HCV/HBV co-infected patients.
- Counsel patients to contact a health care professional immediately if they develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools, as these may be signs of serious liver injury.
- Encourage patients to read the patient information leaflet or [Medication Guide](#) that comes with their DAA prescriptions.
- Report adverse events involving DAAs to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

Data Summary

A search of the [FDA Adverse Event Reporting System \(FAERS\) database](#) and the medical literature for cases reported and literature published between November 22, 2013, and July 18, 2016, identified 24 cases with confirmed reactivation of hepatitis B virus (HBV) infection who were receiving treatment with direct-acting antivirals (DAAs) for the treatment of HCV.¹⁻⁷ HBV reactivation usually occurred within 4-8 weeks, 52 days on average, of starting HCV treatment. Three of the patients decompensated, two of which died and one required hepatic transplantation.

The mechanism through which HBV reactivation occurs with DAAs is currently unknown. These medicines are not known to cause immunosuppression, but HBV reactivation may result from a complex interplay of host immunologic responses in the setting of infection with two hepatitis viruses. HBV reactivation was not reported as an adverse event during the clinical trials supporting the applications for the DAA approvals because HBV co-infection was one of the exclusion criteria. Patients with HBV co-infection were excluded in the initial phase 3 trials to allow a characterization of drug safety, including potential liver adverse reactions, in the presence of one hepatitis virus before conducting a more complicated safety evaluation of the drugs in patients infected with two hepatitis viruses.

Twelve of the 24 cases eventually received antiviral treatment active against HBV, either tenofovir or entecavir. Six cases did not report whether the patients received HBV treatment. The remaining six patients did not receive HBV treatment, and the reports did not contain sufficient information to assess why HBV treatment was not initiated. Treatment for HBV was reported to have been delayed in at least five of the 12 cases, and one patient died. Possible delays in HBV treatment occurred in at least three other cases, and one of these patients required a hepatic transplantation. With HBV treatment, most patients had improvement in HBV DNA, and in other signs and symptoms such as elevated transaminases, and malaise or fatigue.

In eight of the 24 cases, when transaminases started to rise, an adverse drug reaction caused by DAA hepatotoxicity was the initial diagnosis, and the medicines were discontinued. As the condition of patients deteriorated or failed to improve, HBV reactivation was considered among

the likely diagnoses. Thus, a common sequence of events was initiation of DAA-based HCV treatment, rapid drop of HCV RNA to undetectable levels within 1-2 weeks after normalization of transaminase levels (if they were elevated), followed by a rise in HBV DNA with or without increase in transaminases between weeks 4-8.

The patients who developed HBV reactivation were heterogeneous in terms of HCV genotype. These patients were also heterogeneous in terms of baseline HBV disease, fitting into three general categories of patients: those with detectable HBV viral load (n=7), those with positive HBsAg and undetectable HBV viral load (n=4), and those with negative HBsAg and undetectable HBV viral load (n=3). For the remaining 10 patients, HBsAg status was either not known or baseline HBV could not be interpreted.

References

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4. De Monte A, Courjon J, Anty R, Cua E, Naqvi A, Mondain V, et al. Direct-acting antiviral treatment in adults infected with hepatitis C virus: Reactivation of hepatitis B virus coinfection as a further challenge. *J Clin Virol* 2016;78:27-30.
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7. Wang C, Ji D, Chen J, Shao Q, Li B, Liu J, et al. Hepatitis due to reactivation of hepatitis B virus in endemic areas among patients with hepatitis C treated with direct-acting antiviral agents. *Clin Gastroenterol Hepatol*. 2016 Jul 5. pii: S1542-3565(16)30370-6. doi: 10.1016/j.cgh.2016.06.023. [Epub ahead of print].

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