Direct-Acting Antivirals – Safety Communication

- On October 4, 2016, the FDA announced that a new *Boxed Warning* will be added to ***all*** direct-acting antivirals (DAAs) for hepatitis C virus (HCV) infection, regarding the risk of hepatitis B virus (HBV) reactivation.
    - DAAs include: Daklinza™ (daclatasvir), Epclusa® (sofosbuvir/velpatasvir), Harvoni® (ledipasvir/sofosbuvir), Olysio® (simeprevir), Sovaldi® (sofosbuvir), Technivie™ (ombitasvir/paritaprevir/ritonavir), Viekira Pak™ (dasabuvir; ombitasvir/paritaprevir/ritonavir), Viekira XR™ (dasabuvir/ ombitasvir/paritaprevir/ritonavir), and Zepatier™ (elbasvir/grazoprevir).
- HBV can become reactivated in any patient who has a current or previous infection with HBV and is treated with DAAs. In a few cases, HBV reactivation in patients treated with DAAs resulted in serious liver problems or death.
- The *Boxed Warning* will direct healthcare providers to screen and monitor for HBV in all patients receiving DAAs for HCV infection. The Medication Guide will be updated with similar information.
- DAAs are used to treat chronic 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.
- FDA recommendations for healthcare providers:
    - Patients should be screened for evidence of current or prior HBV infection before starting treatment with DAAs by measuring HBsAg and antiHB-c. In patients with serologic evidence of HBV infection, measure baseline HBV DNA prior to DAA treatment.
    - Patients should be monitored using blood tests for HBV flare-ups or reactivation during treatment and post-treatment follow-up.
    - Physicians with expertise in managing HBV infection should be consulted regarding the monitoring and consideration of HBV treatment in HCV/HBV co-infected patients.
- FDA recommendations for patients:
    - Patients should inform their healthcare provider if they have a history of HBV infection, other liver problems, or have human immunodeficiency virus (HIV) infection before being treated for HCV.
    - Patients should not stop taking their DAA medicine without first talking to their health care provider. Stopping therapy could result in the virus becoming less responsive to certain HCV therapies.
    - Patients should contact their healthcare provider immediately if they develop signs and symptoms of liver problems including fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools.
- The new *Boxed Warning* is based on case reports submitted to the FDA and from the published literature of HCV/HBV co-infected patients treated with DAAs from November 2013 to July 2016.

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  - HBV reactivation usually occurred within 4 – 8 weeks, 52 days on average, of starting HCV treatment.
  - Of the 24 identified cases of HBV reactivation, two patients died and one required a liver transplant.
  - 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 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 in the clinical trials submitted for the DAA approvals because patients with HBV co-infection were excluded. 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.