

Drug Class Review Monograph – GPI Class 12 – Antivirals

Review Time Frame: 02/2016 – 04/2017

Previous Class Review: 05/2016

Background:

Antiviral agents are used to treat infections caused by viruses, including, but not limited to, human immunodeficiency virus (HIV), hepatitis B and C viruses, herpes, and influenza A and B viruses.

New treatment guideline recommendations:

- In the 2016 (July, September) and 2017 (April) updates of the hepatitis C virus (HCV) guidelines, the American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) recommends Epclusa for the treatment of all HCV genotypes. In addition, Epclusa and Harvoni are recommended for genotype 5 and 6 individuals with decompensated cirrhosis.
- In the 2016 recommendations for the use of antiretroviral drugs for the treatment and prevention of HIV infection in adults, the International Antiviral Society-USA Panel recommends antiretroviral treatment be started in all individuals with HIV with detectable viremia regardless of CD4 cell count. Optimal treatment regimens are 2 nucleoside reverse transcriptase inhibitors plus an integrase strand transfer inhibitor. For prophylaxis, tenofovir is recommended.

Newly approved drugs:

- Approved 03/01/2016: Odefsey (emtricitabine/rilpivirine/tenofovir alafenamide fumarate) 200/25/25 mg tablets; currently commercially available.
- Approved 04/04/2016: Descovy (emtricitabine/tenofovir alafenamide fumarate) 200/25 mg tablets; currently commercially available.
- Approved 06/28/2016: Epclusa (sofosbuvir/velpatasvir) 400/100 mg tablets; currently commercially available.

Newly approved formulations:

- Approved 07/22/2016: Viekira XR (dasabuvir/ombitasvir/paritaprevir/ritonavir) 200/8.33/50/33.33 mg extended-release tablets; currently commercially available.
- Approved 11/04/2016: Selzentry (maraviroc) 20 mg/mL oral solution; currently commercially available.
- Approved 11/10/2016: Vemlidy (tenofovir alafenamide fumarate) 25 mg tablets; currently commercially available.
- Approved 02/17/2017: ganciclovir 500 mg/250 mL solution for intravenous infusion; anticipated commercial availability unknown.

Newly approved generics:

- Approved 02/17/2016: Sustiva (efavirenz) 600 mg tablets; tentatively available December 2017.

- Approved 04/15/2016: Lexiva (fosamprenavir calcium) 700 mg tablets; tentatively available Q1 2017.
- Approved 08/03/2016: Tamiflu (oseltamivir phosphate) 30 mg, 45 mg, and 75 mg capsules; currently commercially available.
- Approved 09/26/2016: Ziagen (abacavir) 20 mg/mL oral solution; tentatively available first half of 2017.
- Approved 10/06/2016: Virazole (ribavirin) 6 g/vial inhalation solution; currently commercially available.
- Approved 12/27/2016: Kaletra (lopinavir/ritonavir) 80 mg/20 mg/mL oral solution; currently commercially available.

Discontinued drugs:

- None identified

FDA Safety Alerts/black box warnings:

- 10/04/2016: FDA Drug Safety Communication: FDA warns about risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C (refer to page 4 for full detail when applicable).

Pipeline alerts:

Agents pending FDA approval include:

- Isentress (raltegravir), a once-daily formulation proposed for the treatment of HIV-1 infection in combination with other antiretroviral agents in previously untreated adults and those whose virus remains suppressed after treatment with an initial regimen of twice daily raltegravir; PDUFA: 05/27/2017.
- Hepilisav-B (hepatitis B vaccine), a vaccine proposed for immunization against hepatitis B infection in adults; PDUFA: 08/10/2017.
- Glecaprevir/pibrentasvir, a combination direct-acting antiviral therapy proposed for the treatment of patients with HCV genotypes 1-6, including severe renal impairment, compensated cirrhosis, and previous treatment failure with an oral direct-acting antiviral regimen; PDUFA: 08/02/2017.
- Sofosbuvir/velpatasvir/voxilaprevir, a combination direct-acting antiviral therapy proposed for the treatment of patients with HCV genotypes 1-6 in whom direct-acting antiviral therapy failed; PDUFA: 08/08/2017.
- Shingrix (herpes zoster vaccine), a vaccine proposed for the prevention of varicella zoster virus infection (also referred to as herpes zoster or shingles) in patients 50 years of age and older; PDUFA: 10/24/2017.
- Ibalizumab, an IV infusion proposed for the treatment of multi-drug resistant HIV-1 infection in combination with other antiretroviral agents; PDUFA: 01/03/2018.
- Fluarix Quadrivalent (influenza vaccine), a vaccine proposed for active immunization against influenza A and B viruses in patients 6 to 35 months of age; PDUFA: 01/15/2018.
- Dengvaxia (tetravalent dengue vaccine), a vaccine proposed for the prevention of 4 serotypes of dengue fever and dengue hemorrhagic fever in children in endemic countries and travelers visiting affected regions; PDUFA: 03/01/2018.

- Remune (GP120-depleted HIV-1 vaccine), a vaccine proposed for the treatment of HIV-1 infection in pediatric patients; PDUFA: 03/31/2018.

References:

1. AASLD-IDSAs. Recommendations for testing, managing, and treating hepatitis C. <http://www.hcvguidelines.org>. Accessed May 3, 2017.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. URL: <http://www.clinicalpharmacology-ip.com/>. Accessed May 2017.
3. US Script Oracle PBM: Medi-Span[®] Master Drug Data Base. April 2016.
4. Food and Drug Administration. [WWW.FDA.GOV](http://www.fda.gov). Accessed May 2017.
5. Gunthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA Panel. JAMA. 2016; 316(2): 191-210.
6. Envolve Pharmacy Solutions internal pipeline database. Accessed May 2017.

(FDA Drug Safety Communication, continued from page 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

[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. 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.

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.