Hepatitis C Agents
Daklinza (daclatasvir), Epclusa (sofosbuvir & velpatasvir), Harvoni (ledipasvir & sofosbuvir), Sovaldi (sofosbuvir), Mavyret (glecaprevir and pibrentasvir), Pak, Viekira XR (ombitasvir, paritaprevir, ritonavir) and (dasabuvir), Vosevi (sofosbuvir, velpatasvir, & voxilaprevir), Zepatier (elbasvir, grazoprevir)

RATIONALE FOR INCLUSION IN PA PROGRAM

Background
Hepatitis C is a viral disease that causes inflammation of the liver that can lead to diminished liver function or liver failure. Most people infected with hepatitis C virus (HCV) have no symptoms of the disease until liver damage becomes apparent, which may take several years. Some people with chronic HCV infection develop scarring and poor liver function (cirrhosis) over many years, which can lead to complications such as bleeding, jaundice (yellowish eyes or skin), fluid accumulation in the abdomen, infections or liver cancer (1).

Regulatory Status
FDA-approved indications:

1. **Harvoni** is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, and is indicated for the treatment of chronic hepatitis C (CHC) genotype 1, 4, 5 and 6 infection in adults and children 12 – 17 years of age who are at least 35 kg without cirrhosis or with compensated cirrhosis (2).

2. **Epclusa** is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infections (3):
   - Without cirrhosis or with compensated cirrhosis
   - With decompensated cirrhosis for use in combination with ribavirin

3. **Viekira Pak** and **Viekira XR** is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV): (4)
   - Genotype 1b without cirrhosis or with compensated cirrhosis
   - Genotype 1a without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.

4. **Zepatier** is a fixed-dose combination containing elbasvir, a hepatitis C virus (HCV) NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor, and is indicated with or without ribavirin for treatment of chronic HCV genotypes 1 or 4 infection in adults (5).

5. **Daklinza** is a hepatitis C virus (HCV) NS5A inhibitor indicated for use with sofosbuvir, with or without ribavirin, for the treatment of chronic HCV genotype 1 or 3 infection (6).
Hepatitis C Agents

- Daklinza (daclatasvir), Epclusa (sofosbuvir & velpatasvir), Harvoni (ledipasvir & sofosbuvir), Sovaldi (sofosbuvir), Mavyret (glecaprevir and pibrentasvir), Pak, Viekira XR (ombitasvir, paritaprevir, ritonavir) and (dasabuvir), Vosevi (sofosbuvir, velpatasvir, & voxilaprevir), Zepatier (elbasvir, grazoprevir)

6. **Sovaldi** is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. Sovaldi efficacy has been established in subjects with HCV genotype 1, 2, 3, 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection and in pediatric patients 12 years of age and older and weighing at least 35kg with genotype 2 or 3 chronic HCV infection without cirrhosis or with compensated cirrhosis in combination with ribavirin (7).

7. **Ribavirin** is a nucleoside analogue indicated for the treatment of chronic hepatitis C (CHC) virus infection. Ribavirin monotherapy is not effective for the treatment of chronic hepatitis; therefore, Ribavirin capsules must not be used alone (8).

8. **Vosevi** is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, velpatasvir, an HCV NS5A inhibitor, and voxilaprevir, an HCV NS3/4A protease inhibitor, and is indicated for the treatment of adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor. (9)
   - Genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.
   - Additional benefit of VOSEVI over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.

9. **Mavyret** is a fixed-dose combination of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor, and is indicated for the treatment of patients with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis and with compensated cirrhosis (Child-Pugh A). Mavyret is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both (10).

No dose recommendation of Harvoni, Epclusa can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] <30 mL/min/1.73m²) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite (2-3).
**Hepatitis C Agents**

Daklinza (daclatasvir), Epclusa (sofosbuvir & velpatasvir), Harvoni (ledipasvir & sofosbuvir), Sovaldi (sofosbuvir), Mavyret (glecaprevir and pibrentasvir), Pak, Viekira XR (ombitasvir, paritaprevir, ritonavir) and (dasabuvir), Vosevi (sofosbuvir, velpatasvir, & voxilaprevir), Zepatier (elbasvir, grazoprevir)

Viekira Pak, Viekira XR, Vosevi, and Zepatier are contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C) due to potential toxicity. Mavyret is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and contraindicated in patients with severe hepatic impairment (Child-Pugh C) due to potential toxicity (4-5, 9-10).

If Hepatitis C medication is administered with ribavirin, the contraindications to ribavirin also apply to the combination regimen. The primary toxicity of ribavirin is hemolytic anemia. The boxed warning explains that the anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin (8).

There is a boxed warning stating that ribavirin may cause birth defects and fetal death. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month post-treatment follow-up period (8).

All Hepatitis C medications have boxed warning for Hepatitis B virus reactivation, occasionally fulminant, during or after Hepatitis C virus (HCV) therapy which have been reported in HBV/HCV coinfectected patients who were not already on HBV suppressive therapy. In light of these observations, all patients initiating HCV therapy should be assessed for HBV coinfection with testing for HBsAg, anti-HBs, and anti-HBc (11).

**Drug Interactions:**

Harvoni is not recommended in combination with rosuvastatin. Amiodarone is not recommended in combination with Harvoni due to severe bradycardia. Proton pump inhibitors (PPI) can be given with Harvoni but Histamine$_2$ (H$_2$) blockers preferred (2).

Epclusa is not recommended in combination with rosuvastatin in doses over 10mg. Proton pump inhibitors (PPI) can be given with Harvoni but should be given at least 4 hours apart and Histamine$_2$ (H$_2$) blockers should be given 12 hours apart (3).
Hepatitis C Agents

Daklinza (daclatasvir), Epclusa (sofosbuvir & velpatasvir), Harvoni (ledipasvir & sofosbuvir), Sovaldi (sofosbuvir), Mavyret (glecaprevir and pibrentasvir), Pak, Viekira XR (ombitasvir, paritaprevir, ritonavir) and (dasabuvir), Vosevi (sofosbuvir, velpatasvir, & voxilaprevir), Zepatier (elbasvir, grazoprevir)

Safety and effectiveness of Daklinza, Epclusa, Mavyret, Viekira Pak, Viekira XR, Vosevi and Zepatier in children less than 18 years of age have not been established (3-6, 9,10).

Safety and effectiveness of Harvoni and Sovaldi in children less than 12 years of age have not been established (2,7).

Summary

Hepatitis C is a viral disease that causes inflammation of the liver that can lead to diminished liver function or liver failure. Most people infected with hepatitis C virus (HCV) have no symptoms of the disease until liver damage becomes apparent, which may take several years. Safety and effectiveness of Daklinza, Epclusa, Mavyret, Viekira Pak, Viekira XR, Vosevi and Zepatier in children less than 18 years of age have not been established. Safety and effectiveness of Harvoni and Sovaldi in children less than 12 years of age have not been established (2-10, 13).

Prior authorization is required to ensure the safe, clinically appropriate and cost effective use of Daklinza, Epclusa, Harvoni, Mavyret, Sovaldi, Vosevi, Viekira Pak, Viekira XR and Zepatier while maintaining optimal therapeutic outcomes.

References

11. AASLD and IDSA: Recommendations for Testing, Managing, andTreating Hepatitis C; July
**Hepatitis C Agents**

Daklinza (daclatasvir), Epclusa (sofosbuvir & velpatasvir), Harvoni (ledipasvir & sofosbuvir), Sovaldi (sofosbuvir), Mavyret (glecaprevir and pibrentasvir), Pak, Viekira XR (ombitasvir, paritaprevir, ritonavir) and (dasabuvir), Vosevi (sofosbuvir, velpatasvir, & voxilaprevir), Zepatier (elbasvir, grazoprevir)

2017. www.hcvguidelines.org

12. Abergel A, Loustaud-Ratti V, Metivier S et al. Ledipasvir/sofosbuvir for the treatment of patients with chronic genotype 4 or 5 HCV infection. 50th Annual Meeting of the European Association for the Study of the Liver (EASL). April 22-26, 2015; Vienna, Italy.