HEPATITIS C AGENTS

Epclusa (sofosbuvir & velpatasvir), Harvoni (ledipasvir & sofosbuvir), Sovaldi (sofosbuvir), Mavyret (glecaprevir and pibrentasvir), Vosevi (sofosbuvir, velpatasvir, & voxilaprevir), Zepatier (elbasvir, grazoprevir)

Bolded medications are the preferred products

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 adults and pediatric patients 3 years of age and older with chronic hepatitis C (CHC) (2):
   a. Genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis
   b. Genotype 1 infection with decompensated cirrhosis, for use in combination with ribavirin
   c. Genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, for use in combination with ribavirin

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):
   a. Without cirrhosis or with compensated cirrhosis
   b. With decompensated cirrhosis for use in combination with ribavirin

3. 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 (4).
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4. **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 3 years of age and older with genotype 2 or 3 chronic HCV infection without cirrhosis or with compensated cirrhosis in combination with ribavirin (5).

5. **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 (6).

6. **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. (7)
   a. Genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.
   b. 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.

7. **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 adult and pediatric patients 12 years and older or weighing at least 45 kg with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). Mavyret is also indicated for the treatment of adult and pediatric patients 12 years and older or weighing at least 45 kg 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 (8).
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No dose adjustment of Harvoni, Epclusa, or Vosevi is recommended in patients with any degree of renal impairment, including end stage renal disease (ESRD) on dialysis (2-3, 7).

Vosevi and Zepatier are contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C) due to potential toxicity. Mavyret is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) or those with any history of prior hepatic decompensation (4, 7-8).

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 (6).

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 (6).

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 coinfected 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 (9).

Drug Interactions:
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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).

Chronic alcohol use is an important risk factor because alcohol consumption has been associated with more rapid fibrosis progression. Treatment of HCV-infected persons who inject drugs should be delivered in a multidisciplinary care setting with services to reduce the risk of reinfection and for management of the common social and psychiatric comorbidities in this population. Physicians should review alcohol consumption and drug abuse with patients while on hepatitis c medications (9-11).

Safety and effectiveness of Epclusa, Vosevi and Zepatier in children less than 18 years of age have not been established (3-4, 7).

The safety and effectiveness of Harvoni and Sovaldi in pediatric patients less than 3 years of age and for Mavyret in pediatric patients less than 12 years of age have not been established (2,5,8).

**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 Epclusa, Vosevi and Zepatier in children less than 18 years of age have not been established. The safety and effectiveness of Harvoni and Sovaldi in pediatric patients less than 3 years of age and for Mavyret in pediatric patients less than 12 years of age have not been established (2-8, 11).
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Prior authorization is required to ensure the safe, clinically appropriate and cost effective use of Epclusa, Harvoni, Mavyret, Sovaldi, Vosevi, and Zepatier while maintaining optimal therapeutic outcomes.

References

10. 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.