Clinical Policy: Ledipasvir/Sofosbuvir (Harvoni)

Reference Number: PA.CP.PHAR.279
Effective Date: 08/17
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Description
Ledipasvir/sofosbuvir (Harvoni®) is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor.

FDA-Approved Indication
Harvoni is indicated for the treatment of chronic hepatitis C virus (HCV) in:

- Adults with genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis;
- Adults with genotype 1 infection with decompensated cirrhosis, in combination with ribavirin;
- Adults with genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with ribavirin;
- Pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 1, 4, 5, or 6 without cirrhosis or with compensated cirrhosis.

Policy/Criteria
It is the policy of Pennsylvania Health and Wellness ® that Harvoni is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria
*** Provider must submit documentation (including office chart notes and lab results) supporting that member has met all approval criteria ***

A. Chronic Hepatitis C Infection (must meet all)**:**

1. Age ≥ 12 years or body weight ≥35kg;
2. Diagnosis of chronic hepatitis C virus (HCV) infection as evidenced by detectable HCV ribonucleic acid (RNA) levels;
3. Confirmed HCV genotype is 1, 4, 5 or 6;
4. If actively abusing alcohol or IV drugs, or has a history of abuse, has documentation of prescriber counseling regarding the risks of alcohol or IV drug abuse and an offer of a referral for substance use disorder treatment
5. Has all of the following:
   a. Documented quantitative HCV RNA at baseline that was tested within the past 3 months.
   b. Dose not have a life expectancy of less than 12 months due to non-liver-related comorbid conditions.
   c. Has correct or addressed the causes of non-adherence to a previously prescribed Hepatitis C treatment regimen if the recipient has a history of failed treatment due to non-adherence.
   d. Had all potential drug interactions addressed by the prescriber
6. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see Section V Dosage and Administration for reference)*;

7. If member is ≥ 18 years of age and member is without cirrhosis or with compensated cirrhosis (Child-Pugh A): Contraindication or intolerance to Mavyret;or Mavyret isnot AASLD recommended.
8. Has documented completion of
   i. Hepatitis B immunization series or Hepatitis B screening (sAb/sAg and cAb/cAg) AND
   ii. If there is detectable HBV DNA, will be treated for Hepatitis B or if negative for hepatitis BsAb, is being vaccinated against Hepatitis B.AND
   iii. Has a documented HIV screening (HIV Ag/Ab) and if confirmed positive by HIV-1/HIV-2 differentiation immunoassay: Is being treated for HIV or is not being treated for HIV and the medical record documents the rationale for not being treated
9. Has a documented commitment to adherence with the planned course of treatment
10. If prescribed with ribavirin, member has none of the following contraindications:
    a. Pregnancy or possibility of pregnancy - member or partner;
    b. Hemoglobin < 10 g/dL.

Approval duration: up to 24 weeks *(*Approved duration should be consistent with a regimen in Section V Dosage and Administration)*

B. Other diagnoses/indications: Refer to PA.CP.PHAR.57 - Global Biopharm Policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Approval

*** Provider must submit documentation (including office chart notes and lab results) supporting that member has met all approval criteria ***

A. Chronic Hepatitis C Infection (must meet all)**:**

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Dose does not exceed ledipasvir/sofosbuvir 90 mg/400 mg per day (1 tablet/day).

Approval duration: up to a total of 24 weeks*

*(*Approved duration should be consistent with a regimen in Section V Dosage and Administration)*

B. Other diagnoses/indications

1. Refer to PA.CP.PHAR.57 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – PA.CP.PHAR.57 or evidence of coverage documents.

IV. Appendices

Appendix A: Abbreviation Key

ALT: alanine aminotransferase
APRI: AST to platelet ratio
AASLD: American Association for the Study of Liver Diseases
CHC: chronic hepatitis C
FDA: Food and Drug Administration
CTP: Child Turcotte Pugh
FIB-4: Fibrosis-4 index
HBeAg: hepatitis B virus envelope antigen
HBV: hepatitis B virus
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
IDSA: Infectious Diseases Society of America
MRE: magnetic resonance elastography
NS3/4A, NS5A/B: nonstructural protein
Peg-IFN: pegylated interferon
PI: protease inhibitor
RBV: ribavirin
RNA: ribonucleic acid

Appendix B: General Information

- Hepatitis B Reactivation is a Black Box Warning for all direct-acting antiviral drugs for the treatment of HCV. The provider must provide either:
  - Documentation of absence of concurrent HBV infection as evidenced by laboratory values showing absence of hepatitis B virus envelope antigen (HBeAg) and HBV DNA;
  - Documentation that HBV co-infected patient may not be candidates for therapy as evidenced by one of the following:
    - Absence of HBeAg, HBV DNA less than 2,000 international units/mL, and alanine aminotransferase (ALT) level within 1 to 2 times the upper limit of normal;
    - HBeAg-positive and HBV DNA greater than 1,000,000 international units/mL and ALT level within 1 to 2 times the upper limit of normal;
  - Documentation that concurrent HBV infection is being treated (e.g., tenofovir alafenamide, adefovir, entecavir), unless contraindicated or clinically significant adverse effects are experienced.
- The 2016 AASLD/IDSA treatment guideline for HBV consider ALT levels <30 U/L for men and <19 U/L for women as upper limits of normal.
- The 2016 AASLD/IDSA treatment guideline for HBV recommend adults with compensated cirrhosis, even with low levels of viremia (<2,000 IU/mL) be treated with antiviral therapy to reduce the risk of decompensation, regardless of ALT level. The recommendation extends to adults with decompensated cirrhosis be treated with antiviral therapy indefinitely regardless of HBV DNA level, HBeAg status, or ALT level to decrease the risk of worsening liver-related complications.

Appendix C: Direct-Acting Antivirals for Treatment of HCV Infection

Brand Name	Drug Class				
	NS5A Inhibitor	Nucleotide Analog NS5B Polymerase Inhibitor	Non-Nucleoside NS5B Palm Polymerase Inhibitor	NS3/4A Protease Inhibitor (PI)**	CYP3A Inhibitor
Daklinza	Daclatasvir				
Epclusa*	Velpatasvir	Sofosbuvir			
Harvoni*	Ledipasvir	Sofosbuvir			
Olysio				Simeprevir	
Sovaldi		Sofosbuvir			
Technivie*	Ombitasvir			Paritaprevir	Ritonavir
Viekira XR/PAK*	Ombitasvir		Dasabuvir	Paritaprevir	Ritonavir
Zepatier*	Elbasvir			Grazoprevir	

*Combination drugs
**Additional PIs no longer recommended: Victrelis (boceprevir), Incivek (telaprevir)

V. Dosage and Administration

a. **AASLD/IDSA treatment guidelines for chronic hepatitis C infection are updated at irregular intervals; refer to the most updated AASLD/IDSA guideline for most accurate treatment regimen.*

Indication	Dosing Regimen	Maximum Dose	Reference
Genotype 1 CHC:	400 mg/90 mg by PO QD Treatment-naïve adult patients without cirrhosis AND whose HCV viral load is less than 6 million IU/mL for 8 weeks ǂ Treatment-naïve adult patients without cirrhosis AND whose HCV viral load is greater than or equal to 6 million IU/mL for 12 weeks Treatment-experienced with peg-IFN/ RBV adult patients without cirrhosis for 12 weeks Treatment-experienced with NS3 PI*/peg-IFN/RBV adult patient without cirrhosis for 12 weeks Treatment-experienced (with NS3 PI*/peg-IFN/RBV or peg-IFN/RBV) adult patients with compensated cirrhosis: Harvoni plus weight-based	Harvoni (sofosbuvir 400mg / ledipasvir 90mg): 1 tablet per day	1) FDA-approved labeling 2) ǂ AASLD-IDSAhttps://www.hcvguidelines.org/

Indication	Dosing Regimen	Maximum Dose	Reference
	RBV for 12 weeks Or without RBV for 24 weeks ǂ if RBV ineligible Treatment-experienced with sofosbuvir/ RBV with or without peg-IFN without cirrhosis: Harvoni plus weight-based RBV for 12 weeks Treatment-experienced with sofosbuvir/RBV with or without peg-IFN with compensated cirrhosis: Harvoni plus weight-based RBV for 24 weeksǂ		
Genotype 1, 4ǂ, 5ǂ, or 6ǂ CHC with decompensated cirrhosis: Adult patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma	400 mg/90 mg PO QD plus low initial dose of RBV (600mg, increased as tolerated) for 12 weeks Or without RBV for 24 weeks if RBV ineligible	Harvoni (sofosbuvir 400mg / ledipasvir 90mg): 1 tablet per day	1) FDA-approved labeling 2) ǂ AASLD-IDSA https://www.hcvguidelines.org/
Genotype 1, 4, 5, or 6 CHC with decompensated cirrhosis: Adult patients in whom a previous sofosbuvir-containing regimen has failedǂ	400 mg/90 mg PO QD with low initial dose of RBV (600mg, increased as tolerated) for 24 weeks	Harvoni (sofosbuvir 400mg / ledipasvir 90mg): 1 tablet per day	AASLD-IDSA https://www.hcvguidelines.org/
Genotype 1 or 4 CHC and post-liver transplantation: Treatment-naive and treatment-experienced adult patients with or without compensated cirrhosis	400 mg/90 mg PO QD plus RBV for 12 weeks	Harvoni (sofosbuvir 400mg / ledipasvir 90mg): 1 tablet per day	1) FDA-approved labeling 2) AASLD-IDSAhttps://www.hcvguidelines.org/
Genotype 1 or 4 CHC and post-liver transplantation, who are intolerant to	400 mg/90 mg PO QD for 24 weeks	Harvoni (sofosbuvir 400mg / ledipasvir	AASLD-IDSA https://www.hcvguidelines.org/

Indication	Dosing Regimen	Maximum Dose	Reference
RBV or RBV ineligible: Treatment-naïve adult patients with HCV in the allograft, including compensated cirrhosis		90mg): 1 tablet per day	
Genotype 1 or 4 CHC and post-liver transplantation: Treatment-naive and treatment-experienced adult patients with decompensated cirrhosis	400 mg/90 mg PO QD plus low initial dose RBV (600mg, increased as tolerated) for 12 weeks	Harvoni (sofosbuvir 400mg / ledipasvir 90mg): 1 tablet per day	AASLD-IDSA https://www.hcvguidelines.org/
Genotype 1, 4, 5 or 6 CHC with HIV co-infection: Treatment-naïve adult patients without cirrhosis	400 mg / 90 mg PO QD for 12 weeks	Harvoni (sofosbuvir 400mg / ledipasvir 90mg): 1 tablet per day	1) FDA-approved labeling 2) AASLD-IDSA https://www.hcvguidelines.org/
Genotype 4, 5, or 6 CHC: Treatment-naive adult patients with or without compensated cirrhosis	400 mg / 90 mg PO QD for 12 weeks	Harvoni (sofosbuvir 400mg / ledipasvir 90mg): 1 tablet per day	1) FDA-approved labeling 2) AASLD-IDSAhttps://www.hcvguidelines.org/
Genotype 4 CHC: Treatment-experienced adult patients without compensated cirrhosis	400 mg / 90 mg PO QD for 12 weeks	Harvoni (sofosbuvir 400mg / ledipasvir 90mg): 1 tablet per day	1) FDA-approved labeling 2) AASLD-IDSA https://www.hcvguidelines.org/
Genotype 4 CHC: Treatment-experienced adult patients with compensated cirrhosis	400 mg / 90 mg PO QD plus weight-based RBV for 12 weeks Or without RBV for 24 weeks if RBV ineligible‡	Harvoni (sofosbuvir 400mg / ledipasvir 90mg): 1 tablet per day	1) FDA-approved labeling 2) AASLD-IDSAhttps://w

Indication	Dosing Regimen	Maximum Dose	Reference
			ww.hcvguidelines.org/
Genotype 5 or 6 CHC: Treatment-experienced adult patients with or without compensated cirrhosis	400 mg / 90 mg PO QD for 12 weeks	Harvoni (sofosbuvir 400mg / ledipasvir 90mg): 1 tablet per day	1) FDA-approved labeling 2) AASLD-IDSAhttps://www.hcvguidelines.org/

Indication: Pediatric patients (≥ 12 years or weighing at least 35 kg) with chronic HCV infection

Indication	Dosing Regimen	Maximum Dose	
Genotype 1 CHC:	Treatment naïve pediatric patients (≥12 years of >35 kg) without cirrhosis regardless of baseline viral load for 12 weeks Treatment naïve adult or pediatric (≥12 years of >35 kg) patients with compensated cirrhosis for 12 weeks Treatment-experienced with peg-IFN/RBV pediatric (≥12 years of ≥35 kg) without cirrhosis for 12 weeks Treatment-experienced pediatric patients (≥12 years of >35 kg) with compensated cirrhosis for 24 weeks	Harvoni (sofosbuvir 400mg / ledipasvir 90mg): 1 tablet per day	FDA-approved labeling
Genotype 4, 5, or 6 CHC: Treatment-naive or treatment-experienced pediatric (≥12 years of ≥35 kg) patients with or without compensated cirrhosis	400 mg / 90 mg PO QD for 12 weeks	Harvoni (sofosbuvir 400mg / ledipasvir 90mg): 1 tablet per day	FDA-approved labeling

**AASLD/IDSA treatment guidelines for chronic hepatitis C infection are updated at irregular intervals; refer to the most updated AASLD/IDSA guideline for most accurate treatment regimen.*
ǂ *Off-label, AASLD-IDSA guideline-supported dosing regimen*

VI. Product Availability

Tablet: 400 mg sofosbuvir with 90 mg ledipasvir

References

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