Clinical Policy: Ledipasvir/Sofosbuvir (Harvoni)

Reference Number: IL.ERX.SPA.128
Effective Date: 06.01.21
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Line of Business: Illinois Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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(s)

Harvoni is indicated for the treatment of adults and pediatric patients 3 years of age and older with chronic HCV:

- Genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis
- Genotype 1 infection with decompensated cirrhosis, in combination with ribavirin (RBV)
- Genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with RBV

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Harvoni is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of chronic HCV infection as evidenced by detectable HCV RNA levels by quantitative assay in the last 6 months;
   **For treatment-naïve adult members without cirrhosis with genotype 1 and baseline viral load < 6 million IU/mL, Harvoni will be approved for a maximum duration of 8 weeks (see Section V)*
2. Confirmed HCV genotype is 1, 4, 5, or 6;
   **Chart note documentation and copies of lab results are required*
3. Documentation of treatment status of the member (treatment-naïve or treatment-experienced);
4. Documentation of cirrhosis status of the member (no cirrhosis, compensated cirrhosis, or decompensated cirrhosis);
5. Prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious disease specialist, or provider who has expertise in treating HCV based on a certified training program (*see Appendix F)*;
6. Age ≥ 3 years;
7. Member meets one of the following (a or b):
   a. If age between 6 and 11 years, or weight 17 kg to 44 kg: Member has contraindication(s) or clinically significant adverse effects to authorized generic sofosvubir/velpatasvir (Epclusa®) (e.g., patients in whom ribavirin is contraindicated, concurrent administration with carbamazepine, phenytoin, oxcarbazepine, rifampin, tipranavir/ritonavir);
   b. If age ≥ 12 years or weight ≥ 45 kg: Member has contraindication(s) or clinically significant adverse effects to both Mavyret (e.g., concurrent treatment with efavirenz or atazanavir, Child-Pugh B or C hepatic disease) and authorized generic

sofosvubir/velpatasvir (Epclusa®) (e.g., patients in whom ribavirin is contraindicated, concurrent administration with carbamazepine, phenytoin, oxcarbazepine, rifampin, tipranavir/ritonavir);
8. Life expectancy ≥ 12 months with HCV treatment;
9. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see Section V Dosage and Administration for reference)*;
10. Dose does not exceed ledipasvir/sofosbuvir 90 mg/400 mg per day (1 tablet per 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 ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Chronic Hepatitis C Infection (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
   b. Both of the following (i and ii):
      i. Documentation supports that member is currently receiving Harvoni for chronic HCV infection and has recently completed at least 60 days of treatment with Harvoni;
      ii. Confirmed HCV genotype is 1, 4, 5, or 6;
2. Member is responding positively to therapy;
3. Dose does not exceed ledipasvir/sofosbuvir 90 mg/400 mg per day (1 tablet per 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 ERX.PA.01 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 – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AASLD: American Association for the Study of Liver Diseases
FDA: Food and Drug Administration
HBV: hepatitis B virus
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
IDSA: Infectious Diseases Society of America
NS3/4A, NS5A/B: nonstructural protein
PegIFN: pegylated interferon
RBV: ribavirin
RNA: ribonucleic acid

Appendix B: Therapeutic Alternatives

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
sofosvubir/velpatasvir (Epclusa®)	**Genotype 1 through 6:** Without cirrhosis or with compensated cirrhosis, treatment-naïve or treatment-experienced* patient One tablet PO QD for 12 weeks	Adult/Peds ≥ 30 kg: sofosbuvir 400 mg /velpatasvir 100

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
sofosvubir/velpatasvir (Epclusa®)	**Genotype 1 through 6:** With decompensated cirrhosis treatment-naïve or treatment-experienced* patient One tablet PO QD with weight-based RBV for 12 weeks (GT 1, 4, 5, or 6 with decompensated cirrhosis and RBV-ineligible may use: one tablet PO QD for 24 weeks) ‡	mg (one tablet) per day; Peds 17 to < 30 kg: sofosbuvir 200 mg /velpatasvir 50 mg per day; Peds < 17 kg: sofosbuvir 150 mg /velpatasvir 37.5 mg per day
sofosvubir/velpatasvir (Epclusa®)	**Genotype 1, 4, 5, or 6:** With decompensated cirrhosis in whom prior sofosbuvir- or NS5A-based treatment experienced failed One tablet PO QD with weight-based RBV for 24 weeks‡	One tablet (sofosbuvir 400 mg/velpatasvir 100 mg) per day
Mavyret® (glecaprevir /pibrentasvir)	**Genotypes 1 through 6:** Treatment-naïve Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 8 weeks	Adults/Peds age ≥ 12 years or with body weight ≥ 45 kg: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) per day; Peds age 3 years to < 12 years of age with body weight < 20 kg: glecaprevir 150 mg/pibrentasvir 60 mg per day; Peds age 3 years to < 12 years of age with body weight 20 kg to < 30 kg: glecaprevir 200 mg/pibrentasvir 80 mg per day; Peds age 3 years to < 12 years of age with body weight 30 kg to < 45 kg: glecaprevir 250
Mavyret® (glecaprevir /pibrentasvir)	**Genotypes 1, 4, 5, or 6:** Treatment-experienced with IFN/pegIFN + RBV +/- sofosbuvir infection Without cirrhosis: Three tablets PO QD for 8 weeks With compensated cirrhosis: Three tablets PO QD for 12 weeks	
Mavyret® (glecaprevir /pibrentasvir)	**Genotype 1:** Treatment-experienced with NS5A inhibitor without prior NS3/4A protease inhibitor Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks	
Mavyret® (glecaprevir /pibrentasvir)	**Genotype 1:** Treatment-experienced with NS3/4A protease inhibitor without prior NS5A inhibitor Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 12 weeks	

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
		mg/pibrentasvir 100 mg per day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**From clinical trials, treatment-experienced refers to previous treatment with NS3/4A protease inhibitor (telaprevir, boceprevir, or simeprevir) and/or peginterferon/RBV unless otherwise stated*
‡ Off-label, AASLD-IDSA guideline-supported dosing regimen

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): if used in combination with RBV, all contraindications to RBV also apply to Harvoni combination therapy.
- Boxed warning(s): risk of hepatitis B virus reactivation in patients coinfected with HCV and HBV.

Appendix D: Direct-Acting Antivirals (DAAs) 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
Epclusa*	Velpatasvir	Sofosbuvir			
Harvoni*	Ledipasvir	Sofosbuvir			
Mavyret*	Pibrentasvir			Glecaprevir	
Sovaldi		Sofosbuvir			
Viekira PAK*	Ombitasvir		Dasabuvir	Paritaprevir	Ritonavir
Vosevi*	Velpatasvir	Sofosbuvir		Voxilaprevir	
Zepatier*	Elbasvir			Grazoprevir	

**Combination drugs*

Appendix E: General Information

- Hepatitis B Virus Reactivation (HBV) is a Black Box Warning for all direct-acting antiviral drugs for the treatment of HCV. HBV reactivation has been reported when treating HCV for patients co-infected with HBV, leading to fulminant hepatitis, hepatic failure, and death, in some cases. Patients should be monitored for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up, with treatment of HBV infection as clinically indicated.

Appendix F: Healthcare Provider HCV Training

Acceptable HCV training programs and/or online courses include, but are not limited to the following:

- Hepatitis C online course (https://www.hepatitisc.uw.edu/): University of Washington is funded by the Division of Viral Hepatitis to develop a comprehensive, online self-study course for medical providers on diagnosis, monitoring, and management of hepatitis C virus infection. Free CME and CNE credit available.
- Fundamentals of Liver Disease (https://liverlearning.aasld.org/fundamentals-of-liver-disease): The AASLD, in collaboration with ECHO, the American College of Physicians (ACP), CDC, and the Department of Veterans Affairs, has developed Fundamentals of Liver Disease, a free, online CME course to improve providers' knowledge and clinical skills in hepatology.
- Clinical Care Options: http://www.clinicaloptions.com/hepatitis.aspx
- CDC training resources: https://www.cdc.gov/hepatitis/resources/professionals/trainingresources.htm

V. Dosage and Administration

Indication: Patients age ≥ 3 years with chronic HCV infection			
Indication	**Dosing Regimen**	**Maximum Dose**	**Reference**
Genotype 1 chronic HCV infection:	One tablet PO QD for: Treatment-naïve without cirrhosis, who are HIV-uninfected, AND whose HCV viral load is < 6 million IU/mL: for 8 weeks‡ Treatment-naïve without cirrhosis (not meeting the 8 week treatment indication requirements above) or with compensated cirrhosis: for 12 weeks Treatment-experienced* without cirrhosis: for 12 weeks Treatment-experienced* with compensated cirrhosis: Harvoni plus weight-based RBV for 12 weeks (or Harvoni for 24 weeks if RBV-intolerant)	*Weight ≥ 35 kg*: One tablet (sofosbuvir 400 mg / ledipasvir 90 mg) per day *Weight ≥ 17 to < 35 kg*: One tablet (sofosbuvir 200 mg / ledipasvir 45 mg) per day *Weight < 17 kg*: One packet of pellets (sofosbuvir 150 mg / ledipasvir 33.75 mg) per day	1) FDA-approved labeling 2) AASLD-IDSA (updated March 2021)
Genotype 1, 4‡, 5‡, or 6‡ with decompensated cirrhosis	One tablet PO QD plus low initial dose of RBV (600 mg, increased as tolerated) for 12 weeks		1) FDA-approved labeling 2) AASLD-IDSA (updated March 2021)
Genotype 1, 4, 5, or 6 with decompensated cirrhosis: Adult patients in whom a previous sofosbuvir-containing regimen has failed‡	One tablet PO QD with low initial dose of RBV (600 mg, increased as tolerated) for 24 weeks‡		1) FDA-approved labeling 2) AASLD-IDSA (updated March 2021)
Genotype 1, 4, 5‡, or 6‡ post-liver transplantation: Treatment-naive and treatment-experienced* adult patients without cirrhosis, with compensated cirrhosis, or with decompensated cirrhosis	Without cirrhosis or with compensated cirrhosis: One tablet PO QD plus RBV for 12 weeks AASLD recommends patients without cirrhosis or with compensated cirrhosis receive one tablet PO QD for 12 weeks (without ribavirin)‡ With decompensated cirrhosis: One tablet PO QD with RBV for 12 weeks (treatment-naïve)		1) FDA-approved labeling 2) AASLD-IDSA (updated March 2021)

Indication: Patients age ≥ 3 years with chronic HCV infection			
Indication	**Dosing Regimen**	**Maximum Dose**	**Reference**
	or 24 weeks (treatment-experienced*)‡		
Genotype 4, 5, or 6: Treatment-naive and treatment-experienced* adult patients without cirrhosis or with compensated cirrhosis	One tablet PO QD for 12 weeks		1) FDA-approved labeling 2) AASLD-IDSA (updated March 2021)

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.
** Treatment-experienced refers to adult and pediatric subjects have failed a peginterferon alfa +/- ribavirin based regimen with or without an HCV protease inhibitor unless otherwise stated*
‡ Off-label, AASLD-IDSA guideline-supported dosing regimen

VI. Product Availability

- Tablets: 90 mg of ledipasvir and 400 mg of sofosbuvir; 45 mg of ledipasvir and 200 mg of sofosbuvir
- Oral pellets: 45 mg of ledipasvir and 200 mg of sofosbuvir

VII. References

1. Harvoni Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; March 2020. Available at http://www.harvoni.com. Accessed April 15, 2021.
2. American Association for the Study of Liver Diseases/ Infectious Disease Society of America (AASLD-IDSA). HCV guidance: recommendations for testing, managing, and treating hepatitis C. Last updated March 12, 2021. Available at: https://www.hcvguidelines.org/. Accessed April 15, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	04.22.21	05.21
3Q 2021 annual review: removed criterion for sobriety documentation as AASLD recommends to treat all patients with HCV except those with short life expectancy; updated Appendix B Therapeutic Alternatives and section V dosing table; references reviewed and updated.	07.16.21	08.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

be bound by the foregoing terms and conditions, in addition to the Site Use Agreement for Health Plans associated with Envolve Pharmacy Solutions.