Clinical Policy: Ledipasvir/Sofosbuvir (Harvoni)

Reference Number: ERX.SPA.128
Effective Date: 10.01.16
Last Review Date: 08.21
Line of Business: Commercial, 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. Life expectancy ≥ 12 months with HCV treatment;
8. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see Section V Dosage and Administration for reference)*;
9. 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

Not applicable

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			

Brand Name	Drug Class				
	NS5A Inhibitor	Nucleotide Analog NS5B Polymerase Inhibitor	Non-Nucleoside NS5B Palm Polymerase Inhibitor	NS3/4A Protease Inhibitor (PI)**	CYP3A Inhibitor
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	*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)

Indication: Patients age ≥ 3 years with chronic HCV infection			
Indication	**Dosing Regimen**	**Maximum Dose**	**Reference**
	Treatment-experienced* with compensated cirrhosis: Harvoni plus weight-based RBV for 12 weeks (or Harvoni for 24 weeks if RBV-intolerant)		
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‡		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) or 24 weeks (treatment-experienced*)‡		1) FDA-approved labeling 2) AASLD-IDSA (updated March 2021)
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		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.
** 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. 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 converted to new template. Modified diagnosis requirement for HCV RNA levels from over a six-month period to within the last 6 months; updated dosing and administration section per April 2017 AASLD/IDSA guideline; extended initial approval duration up to full regimen; deleted adherence requirement in continued therapy section since appropriate full regimen is provided through initial approval duration per specialist feedback to prevent barriers to adherence; added maximum dose requirement, added documentation of positive response to therapy and continuity of care. Safety criteria was applied according to the safety guidance discussed at CPAC and per EPS.PHARM.31. Exception made to require hep B screening for all patients prior to treatment to ensure that proper risk reduction measures are taking, though this is not specifically addressed in boxed warning.	07.17	08.17
3Q 2018 annual review: removed requirement for HBV verification; added baseline viral load requirement for treatment-naïve adult with GT 1 for determination of treatment duration; added requirement for documentation of previous treatment and cirrhosis status; expanded duration of treatment required for COC from 30 days to 60 days; required verification of genotype for COC; removed requirement for RBV CI; references reviewed and updated.	05.22.18	08.18
3Q 2019 annual review: removed advanced liver disease requirement to align with 2018 AASLD/IDSA hepatitis C treatment guidelines; references reviewed and updated.	05.13.19	08.19
3Q 2020 annual review: updated FDA-approved age to 3 years and older, dosage forms, pediatric dosing information; added new prescriber requirement to include a “provider who has expertise in treating HCV based on a certified training program”; Appendix F (Healthcare Provider HCV Training) added; references reviewed and updated.	05.08.20	08.20
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 section V dosing table; references reviewed and updated.	05.10.21	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.