Clinical Policy: Ledipasvir/Sofosbuvir (Harvoni)

Reference Number: CP.CPA.175
Effective Date: 11.01.16
Last Review Date: 08.21
Line of Business: Commercial

Revision Log

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

Description

Sofosbuvir/ledipasvir (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
- Genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with ribavirin

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.

It is the policy of health plans affiliated with Centene Corporation® 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 serum 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 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. Member must use authorized generic version of Harvoni, unless contraindicated or clinically significant adverse effects are experienced;
4. Documentation of treatment status of the member (treatment-naïve or treatment-experienced);
5. Documentation of cirrhosis status of the member (no cirrhosis, compensated cirrhosis, or decompensated cirrhosis);
6. Prescribed by or in consultation with a gastroenterologist, hepatologist, infectious disease specialist, or provider who has expertise in treating HCV based on a certified training program (*see Appendix F*);
7. Age ≥ 3 years;

8. Member must use Epclusa® (*brand preferred*) or Vosevi®, unless clinically significant adverse effects are experienced or all are contraindicated (*see Appendix E*);
9. Life expectancy ≥ 12 months with HCV treatment;
10. Member agrees to participate in a medication adherence program meeting both of the following components (a and b):
    a. Medication adherence monitored by pharmacy claims data or member report;
    b. Member's risk for non-adherence identified by adherence program or member/prescribing physician follow-up at least every 4 weeks;
11. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (see Section V Dosage and Administration for reference);
12. 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 the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial.

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 Centene benefit or member has previously met initial approval criteria;
    b. Must meet 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/day).

Approval duration: up to a total of 24 weeks*
*(*Approved duration should be consistent with an FDA or AASLD-IDSA recommended regimen)*

B. Other diagnoses/indications (must meet 1 or 2):

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial.

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 – CP.CPA.09 for commercial 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
HCV: hepatitis C virus
HIV: human immunodeficiency 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

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
sofosbuvir/ 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 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
sofosbuvir/ 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)‡	
sofosbuvir/ velpatasvir (Epclusa®)	**Genotype 1 through 6:** Treatment-naïve and treatment-experienced patients, post-liver transplant with compensated cirrhosis or without cirrhosis One tablet PO QD for 12 weeks	
sofosbuvir/ velpatasvir (Epclusa®)	**Genotype 1 through 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
sofosbuvir/ velpatasvir (Epclusa®)	**Genotype 1 through 6:** Treatment-naïve and treatment-experienced patients, post-liver transplant with decompensated cirrhosis	One tablet (sofosbuvir 400 mg /velpatasvir 100 mg) per day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	One tablet PO QD with RBV (starting at 600 mg and increased as tolerated) for 12 weeks (treatment naïve) or 24 weeks (treatment experienced)ǂ	
Vosevi® (sofosbuvir/ velpatasvir/ voxilaprevir)	Genotype 1-6 treatment-experienced with NS5A inhibitor with or without compensated cirrhosis: One tablet PO QD for 12 weeks	One tablet (sofosbuvir 400 mg/ velpatasvir 100 mg/ voxilaprevir 100 mg) per day
Vosevi® (sofosbuvir/ velpatasvir/ voxilaprevir)	Genotype 1a or 3 treatment-experienced with a sofosbuvir-containing regimen without NS5A inhibitor with or without compensated cirrhosis: One tablet PO QD for 12 weeks	One tablet (sofosbuvir 400 mg/ velpatasvir 100 mg/ voxilaprevir 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.
**Treatment-experienced refers to previous treatment with NS3 protease inhibitor (telaprevir, boceprevir, or simeprevir) and/or peginterferon/RBV unless otherwise stated*
ǂ *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 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

- Unacceptable medical justification for inability to use Vosevi (preferred product):
  - In patients indicated for co-administration with amiodarone: serious symptomatic bradycardia in patients taking amiodarone, with cardiac monitoring recommended.

- Acceptable medical justification for inability to use Epclusa (preferred product):
  - In patients indicated for co-administration of Epclusa with ribavirin: contraindications to ribavirin
- 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.
- Child-Pugh Score

	1 Point	2 Points	3 Points
Bilirubin	Less than 2 mg/dL Less than 34 umol/L	2-3 mg/dL 34-50 umol/L	Over 3 mg/dL Over 50 umol/L
Albumin	Over 3.5 g/dL Over 35 g/L	2.8-3.5 g/dL 28-35 g/L	Less than 2.8 g/dL Less than 28 g/L
INR	Less than 1.7	1.7 - 2.2	Over 2.2
Ascites	None	Mild / medically controlled	Moderate-severe / poorly controlled
Encephalopathy	None	Mild / medically controlled Grade I-II	Moderate-severe / poorly controlled. Grade III-IV

Child-Pugh class is determined by the total number of points: A = 5-6 points; B = 7-9 points; C = 10-15 points

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‡		AASLD-IDSA (updated March 2021)
Genotype 1, 4, 5‡, or 6‡ post-liver transplantation: Treatment-naive and treatment-experienced* patients without cirrhosis,	Without cirrhosis or with compensated cirrhosis: One tablet PO QD plus RBV for 12 weeks AASLD recommends patients without cirrhosis or		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**
with compensated cirrhosis, or with decompensated cirrhosis	with compensated cirrhosis receive one tablet PO QD for 12 weeks (without ribavirin)ǂ With decompensated cirrhosis: One tablet PO QD with RBV for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced*)ǂ		
Genotype 4, 5, or 6: Treatment-naïve and treatment-experienced* 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*
ǂ *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; 33.75 mg of ledipasvir and 150 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.
3. CDC.Hepatitis C Q&As for health professionals. Last updated August 7, 2020. Available at: https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm. Accessed April 15, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy converted from "Harvoni NATL11.28.16.docx" to new Centene template.	04.17	05.17
Added expanded indication to adolescent patient population.	04.17	05.17
Annual Review – added requirement of cirrhosis status documentation.	06.17	11.17
Added redirection to Mavyret as an option in addition to Epclusa for Harvoni requests >12 weeks for adult patients. Safety criteria were applied according to the safety guidance discussed at CPAC and endorsed by Centene Medical Affairs. 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.	09.05.17	11.17
3Q 2018 annual review: added age requirement; removed redirection to Epclusa or Mavyret if treatment duration is greater than 12 weeks since parity and redirections no longer shorten duration of tx; removed requirement for HBV verification; revised baseline viral load requirement from all to treatment-naïve adult with GT 1 only for determination of treatment duration; added requirement that prescribed regimen should be consistent with FDA or AASLD recommendations; expanded duration of tx required for COC from 30 days to three quarters of the full regimen; required verification of genotype for COC; references reviewed and updated.	05.22.18	08.18
Removed requirement for advanced fibrosis or other candidacy for therapy following approved clinical guidance; combined with and retired CP.CPA.EX.175 for HNAZ exchange lines of business.	09.03.18	
No clinically significant changes: for age ≥18 and request is for greater than 8 weeks of treatment, added redirection to Mavyret, Zepatier, or authorized generic of Epclusa in line with previously approved clinical guidance.	01.07.19	
3Q 2019 annual review: revised redirection to new approved Mavyret age (12 years) and weight (45 kg) limitations to initial criteria if request is greater than 8 weeks; references reviewed and updated.	05.01.19	08.19
Via CP.PCH.19: CP.CPA.175 retired and combined with HIM to; added requirement that life expectancy ≥ 12 months with HCV treatment and participation in a medication adherence program; 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. RT4: updated Harvoni FDA-approved age (3 years), dosage forms, and pediatric dosing information; updated Mavyret dosing recommendations to 8 weeks total duration of therapy for treatment-naïve HCV with compensated cirrhosis across all genotypes (1-6).	12.03.19	02.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Via CP.PCH.19: RT4: updated redirection for pediatric patients requesting greater than 8 weeks of Harvoni therapy to reflect the pediatric extension for Epclusa to age 6 years or weight ≥ 17 kg.	04.02.20	
3Q 2020 annual review: CP.PCH.19 retired; CP.CPA.175 unretired; added additional redirection to Zepatier for 18 years and older per SDC preferencing; references reviewed and updated.	04.30.20	08.20
Revised redirection to only include Epclusa authorized generic and Mavyret (Harvoni AG 8 weeks and Zepatier no longer preferred); added requirement for use of authorize generic Harvoni; per June SDC and prior clinical guidance.	07.14.20	
Per September SDC and prior clinical guidance for 1/1/21 effective, revised redirection to require brand Epclusa or Vosevi.	09.22.20	
3Q 2021 annual review: updated criteria for age requirement of Epclusa use due to Epclusa's pediatric age expansion; revised medical justification language for not using authorized generic version of Harvoni to "must use" language; added clarification that the brand version of Epclusa is the preferred alternative; included reference to Appendix E with the addition of un/acceptable rationale for bypassing preferred agents; updated Appendix B therapeutic alternatives and section V dosing tables; references reviewed and updated.	07.23.21	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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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