Clinical Policy: Ledipasvir/Sofosbuvir (Harvoni)

Reference Number: CP.CPA.175
Effective Date: 11.01.16
Last Review Date: 08.25
Line of Business: Commercial

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.

It is the policy of health plans affiliated with Centene Corporation® that ledipasvir/sofosbuvir and Harvoni are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of 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, Harvoni will be approved for a maximum duration of 8 weeks (see Section V)*
2. 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*);
3. Age ≥ 3 years;
4. Confirmed HCV genotype is 1, 4, 5, or 6;
   **Chart note documentation and copies of lab results are required*
5. Documentation of treatment status of the member (treatment-naïve or treatment-experienced);
6. Documentation of cirrhosis status of the member (no cirrhosis, compensated cirrhosis, or decompensated cirrhosis);
7. One of the following (a, b, or c):
   a. Member must use **brand Epclusa®**, unless contraindicated or clinically significant adverse effects are experienced (*see Appendix E*);*

b. If member has clinically significant adverse effects or contraindications to brand Epclusa, member must use **authorized generic version of Harvoni®**;
c. Member has clinically significant adverse effects or contraindications to brand Epclusa **and** authorized generic version of Harvoni (*clinical documentation required*);

**Coadministration with omeprazole up to 20 mg is not considered acceptable medical justification for inability to use Epclusa*

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 both of the following (a and b):
    a. Ledipasvir 90 mg/sofosbuvir 400 mg per day;
    b. 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 (must meet all)**:**

1. Member meets one of the following (a, b, or c):
    a. Member must use **brand Epclusa**, if applicable for the requested indication, unless contraindicated or clinically significant adverse effects are experienced (*see Appendix E*);*
    b. If member has clinically significant adverse effects or contraindications to brand Epclusa, member must use **authorized generic version of Harvoni**;
    c. Member has clinically significant adverse effects or contraindications to brand Epclusa **and** authorized generic version of Harvoni (*clinical documentation required*);

    **Coadministration with omeprazole up to 20 mg is not considered acceptable medical justification for inability to use Epclusa*
2. One of the following (a or b):
    a. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (i or ii):
        i. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial; or
        ii. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial; or
    b. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 2a above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial.

II. Continued Therapy

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

1. Member meets one of the following (a, b, or c):

a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
c. Documentation supports that member is currently receiving Harvoni for HCV infection and has recently completed at least 28 days of treatment with Harvoni;

2. Member is responding positively to therapy;
3. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see Section V Dosage and Administration for reference*);
4. Dose does not exceed both of the following (a and b):
   a. Ledipasvir 90 mg/sofosbuvir 400 mg per day;
   b. 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 (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: 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
DAA: direct-acting antiviral
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
SVR12: sustained virologic response at 12 weeks

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 through 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 PO QD with RBV (starting at 600 mg and increased as tolerated) for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced)‡	One tablet (sofosbuvir 400 mg /velpatasvir 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 NS3/4A 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 (HBV) 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			
Vosevi*	Velpatasvir	Sofosbuvir		Voxilaprevir	
Zepatier*	Elbasvir			Grazoprevir	

**Combination drugs*

Appendix E: General Information

- Acceptable medical justification for inability to use Epclusa (preferred product):
  - In patients indicated for co-administration of Epclusa with ribavirin: contraindications to ribavirin
- Unacceptable medical justification for inability to use Epclusa (preferred product):
  - Coadministration with omeprazole up to 20 mg is not considered acceptable medical justification for inability to use Epclusa.
    - Per the Epclusa Prescribing Information: "If it is considered medically necessary to coadminister, Epclusa should be administered with food and taken 4 hours before omeprazole 20 mg."
- HBV reactivation 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.
- Treatment with Harvoni for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL. In the ION-3 trial, patients with a baseline HCV viral load of < 6 million IU/mL and were

treated with Harvoni for 8 weeks achieved SVR-12 at a rate of 97% versus 96% of those treated with Harvoni for 12 weeks.

- 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

Appendix G: Incomplete Adherence and AASLD-IDSA Recommended Management of Treatment Interruptions

- There are minimal data regarding the outcome of patients who have incomplete adherence to direct-acting antiviral (DAA) therapy or the threshold level of adherence below which the incidence of sustained virologic response at 12 weeks (SVR12) is significantly reduced. In general, a treatment interruption of < 7 days is unlikely to impact SVR12.
- There are few data on which to base recommendations regarding how to manage patients who have discontinued DAAs for several days to weeks. The below recommendations are applicable to treatment-naive patients with HCV, without cirrhosis or with compensated cirrhosis*, and receiving either Mavyret or Epclusa*. Patients with prior DAA treatment, or receiving other DAA treatment regimens, or other populations (e.g., patients who are

posttransplant or have decompensated cirrhosis) should be managed in consultation with an expert.

- Interruptions during the first 28 days of DAA therapy:
  - If missed ≤ 7 days, restart DAA therapy immediately and complete therapy for originally planned duration (8 or 12 weeks).
  - If missed ≥ 8 days, restart DAA therapy immediately and obtain HCV RNA test as soon as possible. If HCV RNA is negative, complete originally planned DAA treatment course (8 or 12 weeks). Recommendation to extend DAA treatment for an additional 4 weeks for patients with genotype 3 and/or cirrhosis. If HCV RNA is positive or not obtained, extend DAA treatment for an additional 4 weeks.
- Interruptions after receiving ≥ 28 days of DAA therapy:
  - If missed ≤ 7 days, restart DAA therapy immediately and complete therapy for originally planned duration (8 or 12 weeks).
  - If missed 8-20 consecutive days, restart DAA therapy immediately and obtain HCV RNA test as soon as possible. If HCV RNA is negative, complete originally planned DAA treatment course (8 or 12 weeks). Recommendation to extend DAA treatment for an additional 4 weeks for patients with genotype 3 and/or cirrhosis. If HCV RNA is positive or not obtained, stop treatment and retreat according to the recommendations in the AASLD-IDSA Retreatment Section.
  - If missed ≥ 21 consecutive days, stop DAA treatment and assess for SVR12. If SVR12 not achieved, retreat according to the recommendations in the AASLD-IDSA Retreatment Section.

V. Dosage and Administration

Indication: HCV	Dosing Regimen	Maximum Dose	Reference
Genotype 1	One tablet PO QD for: Treatment-naïve without cirrhosis, HIV-uninfected, AND HCV viral load < 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 December 2023)

Indication: HCV	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 (or Harvoni for 24 weeks if RBV-intolerant)		1) FDA-approved labeling 2) AASLD-IDSA (updated December 2023)
Genotype 1, 4, 5, or 6 with decompensated cirrhosis: Adult patients in whom a previous sofosbuvir- or NS5A inhibitor-based regimen has failed‡	One tablet PO QD with low initial dose of RBV (600 mg, increased as tolerated) for 24 weeks‡		AASLD-IDSA (updated December 2023)
Genotype 1, 4, 5‡, or 6‡ post-liver transplantation: Treatment-naive and treatment-experienced* 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 RBV)‡ With decompensated cirrhosis: One tablet PO QD with low initial dose of RBV (600 mg, increased as tolerated) for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced*)‡		1) FDA-approved labeling 2) AASLD-IDSA (updated December 2023)

Indication: HCV	Dosing Regimen	Maximum Dose	Reference
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 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 who have failed a peginterferon alfa +/- RBV-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.; December 2024. Available at: http://www.harvoni.com/. Accessed April 8, 2025.
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 December 19, 2023. Available at: https://www.hcvguidelines.org/. Accessed May 30, 2025.
3. CDC. Clinical Overview of Hepatitis C. Last updated January 31, 2025. Available at: https://www.cdc.gov/hepatitis-c/hcp/clinical-overview. Accessed May 30, 2025.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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
3Q 2022 annual review: reorganized criteria to clarify intent in steerage; added unacceptable medical justification for inability to use preferred Epclusa in both Appendix E and within criteria; removed co-	07.20.22	08.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
administration with amiodarone as unacceptable rationale for inability to use Vosevi in Appendix E; references reviewed and updated.		
Template changes applied to other diagnoses/indications and continued therapy section.	09.22.22	
3Q 2023 annual review: removed criteria redirections to Vosevi as there are no PI- or AASLD-supported overlapping indications between Vosevi and Harvoni; eliminated adherence program participation criterion since member is already being managed by an HCV-trained specialist and due to competitor analysis; added preferred redirections to other diagnoses/indications initial criteria section; references reviewed and updated.	04.17.23	08.23
3Q 2024 annual review: revised policy/criteria section to also include generic ledipasvir/sofosbuvir; removed qualifier of "chronic" from HCV criteria as AASLD-IDSA recommends treatment of both acute and chronic HCV; removed "preferred" from brand Epclusa redirection; added Appendix G for guidance on incomplete adherence and AASLD-IDSA recommended management of treatment interruptions; references reviewed and updated.	05.30.24	08.24
3Q 2025 annual review: for continued therapy criteria, added "Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen"; references reviewed and updated. For continued therapy criteria, revised option for treatment duration minimum from 60 days to 28 days and removed requirement for specific confirmed genotype.	07.15.25	08.25

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.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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