Clinical Policy: Ledipasvir/Sofosbuvir (Harvoni)

Reference Number: CP.PHAR.279
Effective Date: 09.16
Last Review Date: 08.23
Line of Business: 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.

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, 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. Age ≥ 3 years;
6. One of the following (a, b, or c):
   a. Member must use **Mavyret®** or **sofosbuvir/velpatasvir (Epclusa®) (*authorized generic preferred*)**, unless clinically significant adverse effects are experienced or both are contraindicated (*see Appendix E)*;*

b. If member has clinically significant adverse effects or contraindications to both Mavyret and sofosbuvir/velpatasvir (Epclusa) (*authorized generic preferred*), member must use **authorized generic version of Harvoni®** (*see Appendix E*);
c. Member has clinically significant adverse effects or contraindications to Mavyret, sofosbuvir/velpatasvir (Epclusa) (*authorized generic preferred*), **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*

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 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 use **Mavyret** or **sofosbuvir/velpatasvir (Epclusa) (*authorized generic preferred*),** if applicable for the requested indication, unless clinically significant adverse effects are experienced or both are contraindicated (*see Appendix E)*;*
   b. If member has clinically significant adverse effects or contraindications to both Mavyret and sofosbuvir/velpatasvir (Epclusa) (*authorized generic preferred*), member must use **authorized generic version of Harvoni** (*see Appendix E*);
   c. Member has clinically significant adverse effects or contraindications to Mavyret, sofosbuvir/velpatasvir (Epclusa) (*authorized generic preferred*), **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.PMN.255 for Medicaid; 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.PMN.16 for Medicaid; 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.PMN.53 for Medicaid.

II. Continued Therapy

A. Chronic 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. 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 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.PMN.255 for Medicaid; 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.PMN.16 for Medicaid; 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.PMN.53 for Medicaid.

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 policies – CP.PMN.53 for Medicaid 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 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	One tablet (sofosbuvir 400 mg /velpatasvir 100 mg) per day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	weeks (treatment-naïve) or 24 weeks (treatment-experienced)‡	
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 mg/pibrentasvir 100 mg per day
Mavyret® (glecaprevir /pibrentasvir)	**Genotypes 1, 4, 5, or 6:** Treatment-experienced with IFN/pegIFN, RBV and/or sofosbuvir 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	
Mavyret® (glecaprevir /pibrentasvir)	**Genotypes 1 through 6:** Treatment-naïve or treatment-experienced, post-liver or kidney transplantation without cirrhosis or with compensated cirrhosis Three tablets PO QD for 12 weeks (A 16-week treatment duration is recommended in genotype 1-infected patients who are NS5A inhibitor*	

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	experienced without prior treatment with an NS3/4A protease inhibitor)	

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			
Viekira Pak*	Ombitasvir		Dasabuvir	Paritaprevir	Ritonavir
Vosevi*	Velpatasvir	Sofosbuvir		Voxilaprevir	
Zepatier*	Elbasvir			Grazoprevir	

**Combination drugs*

Appendix E: General Information

- Acceptable medical justification for inability to use Mavyret (preferred product):
  - Moderate or severe hepatic impairment (Child-Pugh B or C) or those with any history of prior hepatic decompensation: use of Mavyret is not recommended as postmarketing cases of hepatic decompensation/failure have been reported in these patients.
  - Drug-drug interactions with the following agents:
    - Atazanavir
    - Efavirenz
- Acceptable medical justification for inability to use Epclusa (preferred product):
  - In patients indicated for co-administration of Epclusa with RBV: contraindications to RBV.

- 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

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose	Reference
Genotype 1 chronic HCV infection:	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	*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	1) FDA-approved labeling 2) AASLD-IDSA (updated October 2022)

Indication	Dosing Regimen	Maximum Dose	Reference
	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 < 17 kg*: One packet of pellets (sofosbuvir 150 mg / ledipasvir 33.75 mg) per day	
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 October 2022)
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 October 2022)
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		1) FDA-approved labeling 2) AASLD-IDSA (updated October 2022)

Indication	Dosing Regimen	Maximum Dose	Reference
	QD with low initial dose of RBV (600 mg, increased as tolerated) 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 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.; March 2020. Available at: http://www.harvoni.com. Accessed April 21, 2023.
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 October 24, 2022. Available at: https://www.hcvguidelines.org/. Accessed May 5, 2023.
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 May 5, 2023.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2019 annual review: revised redirection to new approved Mavyret age (12 years old) and weight limitations (45 kg) in initial criteria; removed documented sobriety from alcohol and illicit IV drugs for ≥ 6 months prior to starting therapy; references reviewed and updated.	06.26.19	08.19
RT4: updated Harvoni FDA-approved age (3 years), dosage forms, and pediatric dosing information; updated Mavyret dosing	10.03.19	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
recommendations to 8 weeks total duration of therapy for treatment-naïve HCV with compensated cirrhosis across all genotypes (1-6).		
Added new prescriber requirement to include a "provider who has expertise in treating HCV based on a certified training program"; for Harvoni requests for greater than 8 weeks or treatment added preferencing for AG Epclusa or Mavyret; removed redirection to Mavyret based on contraindications criteria; Appendix F (Healthcare Provider HCV Training) added.	12.17.19	02.20
Per March SDC and prior clinical guidance, preferencing revised to require AG Epclusa for age 6 to 11 years, or weight 17 kg to 44 kg; revised to require Mavyret or AG Epclusa for age 12 years or older, or weight at least 45 kg .	03.03.20	
3Q 2020 annual review: no significant changes; Appendix B, Appendix D, and Dosage and Administration tables updated; references reviewed and updated.	04.30.20	08.20
3Q 2021 annual review: updated criteria for age requirement of Epclusa & Mavyret use due to their pediatric age expansions; revised medical justification language for not using authorized generic version of Harvoni to "must use" language; included reference to Appendix E with addition of contraindications that would warrant bypassing preferred agents; updated Appendix B therapeutic alternatives and section V dosing tables; references reviewed and updated.	07.23.21	08.21
Reorganized criteria to clarify intent in steerage.	01.11.22	
3Q 2022 annual review: no significant changes; added unacceptable rationale for not using preferred Epclusa within criteria (also found within Appendix E); references reviewed and updated.	07.20.22	08.22
Template changes applied to other diagnoses/indications and continued therapy section.	09.20.22	
3Q 2023 annual review: removed prescriber specialty criterion per Medicaid plan requests; eliminated adherence program participation criterion due to competitor analysis; added preferred redirections to other diagnoses/indications initial criteria section; references reviewed and updated.	05.31.23	08.23

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.