Clinical Policy: Ledipasvir/Sofosbuvir (Harvoni)

Reference Number: GA.PMN.13
Effective Date: 12/16
Last Review Date: 10/2022 Revision Log
Line of Business: Medicaid

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 sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and ledipasvir, an HCV NS5A inhibitor.

FDA Approved Indication(s)
Harvoni is indicated for the treatment of adult and pediatric patients 3 years of age and older with chronic HCV in:

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

I. Approval Criteria
*** Provider must submit documentation (including office chart notes and lab results) supporting that member has met all approval criteria ***

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

1. Diagnosis of chronic hepatitis C virus (HCV) infection as evidenced by detectable HCV ribonucleic acid (RNA) levels 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 labs results are required
3. Documentation of the treatment status of the patient (treatment-naïve or treatment-experienced);
4. Documentation of cirrhosis status of the patient (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 (*in Section III Dosage and Administration)*;
9. Member is hepatitis B virus (HBV) negative, or if positive, documentation that concurrent HBV infection is being treated (e.g., tenofovir alafenamide, adefovir, entecavir), unless contraindicated or clinically significant adverse effects are experienced (*see Appendix E*);
10. If prescribed with ribavirin, member has none of the following contraindications:
    a. Pregnancy or possibility of pregnancy - member or partner;
    b. For Rebetol: creatinine clearance < 50 mL/min;
    c. Hypersensitivity to ribavirin;
    d. Coadministration with didanosine;
    e. Significant/unstable cardiac disease;
    f. Hemoglobinopathy (e.g., thalassemia major, sickle cell anemia);
    g. Hemoglobin < 8.5 g/dL.

Approval duration: up to a total of 24 weeks*
*(*Approved duration should be consistent with a regimen in in Section III Dosage and Administration)*

B. Other diagnoses/indications: Refer to CP.PHAR.53 – No Coverage Criteria/Off-Label Use Policy if diagnosis is NOT specifically listed under section I.

II. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AASLD: American Association for the Study of Liver Diseases
APRI: AST to platelet ratio
CTP: Child Turcotte Pugh
CrCl: creatinine clearance
FDA: Food and Drug Administration
FIB-4: Fibrosis-4 index
MRE: magnetic resonance elastography
NS3/4A, NS5A/B: nonstructural protein
Peg-IFN: pegylated interferon
PI: protease inhibitor
RBV: ribavirin
RNA: ribonucleic acid

HCC: hepatocellular carcinoma
HCV: hepatitis C virus
IDSA: Infectious Diseases Society of America

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	One tablet (Adult/Peds ≥ 30 kg: sofosbuvir 400 mg /velpatasvir 100 mg; Peds 17 to 29 kg: sofosbuvir 200 mg /velpatasvir 50 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 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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Mavyret® (glecaprevir /pibrentasvir)	**Genotypes 1 through 6:** Treatment-naïve Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 8 weeks	Mavyret: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) per day
Mavyret® (glecaprevir /pibrentasvir)	**Genotypes 1, 4, 5, or 6:** Treatment-experienced with IFN/pegIFN + RBV +/- sofosbuvir Without cirrhosis: Three tablets PO QD for 8 weeks With compensated cirrhosis: Three tablets PO QD for 12 weeks	Mavyret: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) per day
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 300 mg/pibrentasvir 120 mg (3 tablets) per day
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 300 mg/pibrentasvir 120 mg (3 tablets) per day
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	Mavyret: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) per day

Theraputic alternatives are listed as Brand Name® (generic) when the drug is a available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

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
Daklinza	Daclatasvir				
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 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."
- Hepatitis B Virus (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

III. 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	*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 /	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* 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)	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 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, 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-naïve and treatment-experienced* patients without cirrhosis or	One tablet PO QD for 12 weeks		FDA-approved labeling

Indication: Patients age ≥ 3 years with chronic HCV infection			
Indication	**Dosing Regimen**	**Maximum Dose**	**Reference**
with compensated cirrhosis			

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.
** NS3 protease inhibitor = telaprevir, boceprevir, or simeprevir*
*** Treatment-experienced refers to previous treatment with peginterferon/RBV unless otherwise stated*
ǂ Off-label, AASLD-IDSA guideline-supported dosing regimen

IV. Product Availability

- Tablet: 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

V. References

1. Harvoni Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; March 2020. Available at http://www.harvoni.com. Accessed May 5, 2022.
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 September 29, 2021. Available at: https://www.hcvguidelines.org/. Accessed May 5, 2022.
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, 2022.

Reviews, Revisions, and Approvals	Date	Approval Date
New policy created, split from CP.PHAR.17 Hepatitis C Therapies policy. HCV RNA levels over six-month period added to confirm infection is chronic.Life expectancy "≥12 months if HCC and awaiting transplant" is modified to indicate "≥12 months with HCV therapy." Testing criteria reorganized by "no cirrhosis"/"cirrhosis" consistent with the regimen tables; HCC population is included under "cirrhosis" and broadened to incorporate HCC amenable to curative measures (resection, ablation, transplant). Methods to diagnose fibrosis/cirrhosis are modified to require presence of HCC, liver biopsy or a combination of one serologic and one radiologic test. Serologic and radiologic tests are updated and correlated with METAVIR per Appendix B. Removed creatinine clearance restriction – not a contraindication. Criteria added excluding post-liver transplantation unless regimens specifically designate. Dosing regimens are presented in Appendix	08/16	09/16

Reviews, Revisions, and Approvals	Date	Approval Date
D and E per AASLD guidelines and FDA-approved indications. The initial approval period is shortened to 8 weeks.		
Removed criteria regarding medication prescribed by a specialist Remove criteria regarding having HCC or advanced liver disease Removed criteria regarding medication adherence program Removed criteria regarding sobriety from alcohol/illicit drugs	10/16	10/2016
Added availability of full course of therapy as initial therapy consistent with appendix recommendation for initial criteria Removed continuation criteria	4/17	4/17
Added pediatric (≥12 years or ≥35 kg) indication expansion for GT 1,4,5,6	6/17	6/17
Added preferencing information requiring Mavyret for FDA-approved indications. Added preferencing for pediatric member for Harvoni since Mavyret does not have a pediatric indication. Added requirement for Hep B screening for all patients prior to treatment.	9/17	9/17
Annual review. No changes made.	3/18	3/18
Changed current Georgia policy templates to corporate standard templates for drug coverage criteria to meet corporate compliance. Changes/revisions included; new formatting, font size, use of standard policy language for each section of policy, and rearranged order of certain steps in criteria and sections. Added new preferred treatment tables that includes dosage and frequency based on genotype for Mavyret. Removed background sections. Updated general information and contraindication section to be consistent with corporate HCV policies.	2/21/19	2/19
Annual review. Added pediatric age to FDA Approved Indication Section. Added specification for Mavyret preferencing based on pediatric age or weight. Combined contraindication section to age/weight preferencing of Mavyret. In the initial approval criteria, changed RNA detectable period from "over a 6 month period" to "in the last 6 months" for infection diagnosis.	10/19	10/19
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). Added preferencing for AG Epclusa or Mavyret; removed redirection to Mavyret based on contraindications criteria. 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 or older or weight at least 45 kg . Updated general information section. Updated order of all other Appendices. Updated references.	4/2020	4/2020
Appendix B and Dosage and Administration tables updated; References reviewed and updated.	7/2020	7/2020

Reviews, Revisions, and Approvals	Date	Approval Date
Annual review. Added Mayvret and Vosevi to Appendix D-Direct Acting Antivirals for Treatment of HCV infection and removed Olysio, Technivie, and Viekira XR as these were previously removed from the market. Changed Centene Logo to PSHP Logo. References reviewed and updated	4/2021	4/2021
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.	7/2021	7/2021
Removed preferencing for authorized generic Harvoni. Updated criteria for age requirement of Epclusa & Mavyret use due to their pediatric age expansions.	1/2022	1/2022
3Q 2022 annual review. References reviewed and updated	7/2022	7/2022
Added unacceptable rationale for not using preferred Epclusa within criteria also within Appendix E; Added "clinical documentation required" to initial criteria option for trial and failure of Mavyret, sofosbuvir/velpatasvir (Epclusa) (*authorized generic preferred*), and authorized generic version of Harvoni. Minor font updates.	10/2022	10/2022

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.

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.