Clinical Policy: Ledipasvir/Sofosbuvir (Harvoni)

Reference Number: CP.PCH.19
Effective Date: 11.01.16
Last Review Date: 02.20
Line of Business: Commercial, HIM

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;
2. Documentation of treatment status of the member (treatment-naïve or treatment-experienced);
3. Documentation of cirrhosis status of the member (no cirrhosis, compensated cirrhosis, or decompensated cirrhosis);
4. Prescribed by or in consultation with a gastroenterologist, hepatologist or infectious disease specialist, or provider who has expertise in treating HCV based on a certified training program (*see Appendix F*);
5. Age ≥ 3 years;
6. Member meets one of the following (a or b):*
   a. HCV genotype is 1 and documentation of baseline viral load is provided;
   b. HCV genotype is 4, 5, or 6;
   **Chart note documentation and copies of lab results are required*
7. Member meets one of the following (a or b):
   a. Age < 6 years;

b. For age ≥ 6 years or weight ≥ 17 kg, member meets one of the following (i or ii):
   i. Request is for 8 weeks only;
   ii. If request is for greater than 8 weeks of treatment: member must use one of the following, unless contraindicated or clinically significant adverse effects are experienced (1 or 2):
      1) If age between 6 and 11 years, or weight between 17 kg and 44 kg, member must use sofosbuvir/velpatasvir (Epclusa®) (*authorized generic preferred*);
      2) If age ≥ 12 years or weight ≥ 45 kg: member must use Mavyret™ or sofosbuvir/velpatasvir (Epclusa®) (*authorized generic preferred*);
8. Life expectancy ≥ 12 months with HCV treatment;
9. 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;
10. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (see Section V Dosage and Administration for reference);
11. Dose does not exceed ledipasvir/sofosbuvir 90 mg/400 mg (1 tablet) per day.

Approval duration:
Age ≥ 12 years or weight ≥ 45 kg: up to a total of 8 weeks*
*(*use Mavyret or authorized generic Epclusa for requests greater than 8 weeks in duration)*
Age < 18 years: 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 and HIM.PHAR.21 for health insurance marketplace.

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 (1 tablet) per 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 and HIM.PHAR.21 for health insurance marketplace.

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 and HIM.PHAR.21 for health insurance marketplace 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
Epclusa® (sofosbuvir/ velpatasvir)	**Genotype 1, 4, 5, or 6:** Without cirrhosis or with compensated cirrhosis, treatment-naïve or pegIFN/ RBV-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
Epclusa® (sofosbuvir/ velpatasvir)	**Genotype 1, 4, 5, or 6:** With decompensated cirrhosis treatment-naïve or treatment-experienced* patient One tablet PO QD with weight-based RBV for 12 weeks	One tablet (Adult/Peds ≥ 30 kg: sofosbuvir 400 mg /velpatasvir 100 mg; Peds 17 to 29 kg: sofosbuvir 200 mg

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	(GT 1, 4, 5, or 6 with decompensated cirrhosis and RBV-ineligible may use: one tablet PO QD for 24 weeks) ǂ	/velpatasvir 50 mg) per day
Epclusa® (sofosbuvir/ velpatasvir)	**Genotype 1, 4, 5, or 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
Epclusa® (sofosbuvir/ velpatasvir)	**Genotype 1b:** With compensated cirrhosis or without cirrhosis and non-NS5A inhibitor, sofosbuvir-containing regimen-experienced One tablet PO QD for 12 weeks	One tablet (sofosbuvir 400 mg /velpatasvir 100 mg) per day
Mavyret™ (glecaprevir/ pibrentasvir)	**Genotype 1, 4, 5, or 6:** Treatment-naive Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 8 weeks	Three tablets (glecaprevir 300 mg/ pibrentasvir 120 mg) per day
Mavyret™ (glecaprevir/ pibrentasvir)	**Genotype 1, 4, 5, or 6:** Treatment-experienced with IFN/pegIFN + RBV Without cirrhosis: Three tablets PO QD for 8 weeks With compensated cirrhosis: Three tablets PO QD for 12 weeks	Three tablets (glecaprevir 300 mg/ pibrentasvir 120 mg) per day
Mavyret™ (glecaprevir/ pibrentasvir)	**Genotypes 1:** Treatment-experienced with sofosbuvir Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 12 weeks	Three tablets (glecaprevir 300 mg/ pibrentasvir 120 mg) per day
Mavyret™ (glecaprevir/ pibrentasvir)	**Genotypes 4, 5, or 6:** Treatment-experienced with sofosbuvir Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 12 weeks	Three tablets (glecaprevir 300 mg/ pibrentasvir 120 mg) per day
Mavyret™ (glecaprevir/ pibrentasvir)	**Genotype 1:** Without cirrhosis or with compensated cirrhosis:	Three tablets (glecaprevir 300

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Three tablets PO QD for 16 weeks	mg/ pibrentasvir 120 mg) per day
Mavyret™ (glecaprevir/ pibrentasvir)	**Genotype 1:** Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 12 weeks	Three tablets (glecaprevir 300 mg/ pibrentasvir 120 mg) per day
Mavyret™ (glecaprevir/ pibrentasvir)	**Genotype 1, 4, 5, or 6:** Three tablets PO QD for 12 weeks	Three tablets (glecaprevir 300 mg/ pibrentasvir 120 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
Daklinza	Daclatasvir				
Epclusa*	Velpatasvir	Sofosbuvir			
Harvoni*	Ledipasvir	Sofosbuvir			
Mavyret*	Pibrentasvir			Glecaprevir	
Olysio				Simeprevir	
Sovaldi		Sofosbuvir			
Technivie*	Ombitasvir			Paritaprevir	Ritonavir
Viekira XR/PAK*	Ombitasvir		Dasabuvir	Paritaprevir	Ritonavir
Vosevi*	Velpatasvir	Sofosbuvir		Voxilaprevir	
Zepatier*	Elbasvir			Grazoprevir	

*Combination drugs

Appendix E: General Information

- Hepatitis B Virus Reactivation (HBV) is a Black Box Warning for all direct-acting antiviral drugs for the treatment of HCV. HBV reactivation has been reported when treating HCV for patients co-infected with HBV, leading to fulminant hepatitis, hepatic failure, and death, in some cases. Patients should be monitored for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up, with treatment of HBV infection as clinically indicated.
- 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
- 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 AND whose HCV viral load is less than 6 million IU/mL: for 8 weeks (12 weeks for black and/or HIV-coinfected patients)ǂ Treatment-naïve with compensated cirrhosis: for 12 weeks Treatment-experienced with pegIFN/ RBV without cirrhosis: for 12 weeks Treatment-experienced with compensated cirrhosis: for 24 weeks Treatment-experienced with pegIFN/ RBV with compensated cirrhosis: Harvoni plus weight-based RBVǂ for 12 weeks Treatment-experienced with NS3 PI*+/-pegIFN/RBV without cirrhosis for 12 weeks Treatment-experienced with NS3 PI*+/- pegIFN/RBV adult patients with compensated cirrhosis: Harvoni plus weight-based RBV for 12 weeks Treatment-experienced with sofosbuvir (but not with simeprevir) without cirrhosis: Harvoni plus weight-based RBV 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 May 2018)

Indication: Patients age ≥ 3 years with chronic HCV infection			
Indication	**Dosing Regimen**	**Maximum Dose**	**Reference**
Genotype 1, 4‡, 5‡, or 6‡ with decompensated cirrhosis: patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma	One tablet PO QD plus low initial dose of RBV (600 mg, increased as tolerated) for 12 weeks Or without RBV for 24 weeks if RBV ineligible	*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 May 2018)
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 May 2018)
Genotype 1 or 4 post-liver transplantation: Treatment-naive and treatment-experienced patients without cirrhosis, with compensated cirrhosis, or with decompensated cirrhosis	One tablet PO QD plus RBV for 12 weeks		1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)
Genotype 4, 5, or 6: Treatment-naive patients with or without compensated cirrhosis	One tablet PO QD for 12 weeks		1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)

Indication: Patients age ≥ 3 years with chronic HCV infection			
Indication	**Dosing Regimen**	**Maximum Dose**	**Reference**
Genotype 4: Treatment-experienced** patients without compensated cirrhosis	One tablet PO QD 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 May 2018)
Genotype 4: Treatment-experienced** patients with compensated cirrhosis	One tablet PO QD plus weight-based RBV for 12 weeks		1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)
Genotype 5 or 6: Treatment-experienced** patients with or without compensated cirrhosis	One tablet PO QD for 12 weeks		1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)

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

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.; August 2019. Available at http://www.harvoni.com/. Accessed September 5, 2019.
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 May 24, 2018. Available at: https://www.hcvguidelines.org/. Accessed April 30, 2019.
3. Wirth S, Gonzalez-Peralta R, Rosenthal P, et al. Sofosbuvir-Containing Regimens are Safe and Effective in Adolescents with Chronic hepatitis C Infection. The 26th Annual Meeting of the Asian pacific Association for the Study of the Liver (APASL) in February 15-19, 2017 in Shanghai, China.

4. Squires JE, Balisteri WF. Hepatitis C Virus Infection in Children and Adolescents. Hepatology Communications 2017; 1(2): 87-98.
5. Wolitski R. When it comes to curing hepatitis c, your health care provider may not need to be a specialist. U.S. Department of Health & Human Services. Last updated September 20, 2017. Available at: https://www.hhs.gov/hepatitis/blog/2017/09/20/study-calls-for-expansion-of-hepatitis-c-treatment.html. Accessed October 30, 2019.
6. CDC. Viral hepatitis: Q&As for health professionals. Last updated July 2, 2019. Available at: https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm. Accessed October 30, 2019.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created; per SDC and prior clinical guidance added HIM line of business to existing Commercial policy (modified policy number to CP.PCH.19, retired HIM.PA.SP3 and CP.CPA.175); added requirement that life expectancy ≥ 12 months with HCV treatment and participation in a medication adherence program.	12.03.19	02.20
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).	11.07.19	02.20
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	

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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