Clinical Policy: Ledipasvir/Sofosbuvir (Harvoni)

Reference Number: CP.PHAR.279
Effective Date: 09/16
Last Review Date: 05/17

Coding Implications
Revision Log

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

Description
The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for ledipasvir/sofosbuvir (Harvoni®).

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. Initial 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. Prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious disease specialist;
2. Age ≥ 12 years or body weight ≥35kg;
3. Diagnosis of chronic hepatitis C virus (HCV) infection as evidenced by detectable HCV ribonucleic acid (RNA) levels over a six-month period;
4. Confirmed HCV genotype is 1, 4, 5 or 6;
5. Life expectancy ≥ 12 months with HCV treatment;
6. Documented sobriety from alcohol and illicit IV drugs for ≥ 6 months prior to starting therapy, if applicable;
7. Advanced liver disease defined as a or b:
   a. Advanced fibrosis indicated by i or ii:
      i. Liver biopsy showing a METAVIR score of F3 or equivalent (Knodell, Scheuer, Batts-Ludwig – F3; Ishak – F4/5);
      ii. One serologic test and one radiologic test showing an equivalent score to METAVIR F3 per Appendix B;
   b. Cirrhosis indicated by i, ii or iii:
      i. Hepatocellular carcinoma (HCC) that is amenable to resection, ablation or transplant;
      ii. Liver biopsy showing a METAVIR score of F4 or equivalent (Knodell, Scheuer, Batts-Ludwig – F4; Ishak - F5/6);
      iii. Both of the following:
         a) One serologic test showing an equivalent score to METAVIR F4 per Appendix B;
         b) One radiologic test showing an equivalent score to METAVIR F4 per Appendix B or other radiologic test showing evidence of cirrhosis (e.g., portal hypertension);

8. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see Appendix D and E for reference)*;
9. If member is ≥ 18 years of age, has a contraindication or intolerance to the following preferred medication(s):
    a. If genotype 1a, 1b and 4: Zepatier and Epclusa *(Zepatier is the preferred agent; Eplcusa should be used if Zepatier is contraindicated);*
    b. If genotype 5 and 6: Epclusa;
10. Member agrees to participate in a medication adherence program meeting both of the following components:
    a. Medication adherence monitored by pharmacy claims data or member report;
    b. Member's risk monitored at least every 4 weeks;
11. If prescribed with ribavirin, member has none of the following contraindications:
    a. Pregnancy or possibility of pregnancy - member or partner;
    b. Hypersensitivity to ribavirin;
    c. Coadministration with didanosine;
    d. Significant/unstable cardiac disease;
    e. Hemoglobinopathy (e.g., thalassemia major, sickle cell anemia);
    f. Hemoglobin < 8.5 g/dL.

Approval duration: Up to a total of 24 weeks*
*(*Approved duration should be consistent with a regimen in Appendix D or E)*

B. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy.

II. Continued Approval

*** 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. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Pharmacy claims support adherence to therapy;
3. If prescribed with ribavirin, member has none of the following reasons to discontinue therapy:
    a. Pregnancy or possibility of pregnancy - member or partner;
    b. Hypersensitivity to ribavirin;
    c. Coadministration with didanosine;
    d. Significant/unstable cardiac disease;
    e. Hemoglobinopathy (e.g., thalassemia major, sickle cell anemia);
    f. Hemoglobin < 8.5 g/dL.

Approval duration: Up to a total of 24 weeks*
*(*Approved duration should be consistent with a regimen in Appendix D or E)*

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy; or
2. Refer to CP.PHAR.57 - Global Biopharm Policy**.**

Background

Description/Mechanism of Action:

Harvoni is a fixed-dose combination tablet containing ledipasvir and sofosbuvir for oral administration. Ledipasvir is an HCV NS5A inhibitor and sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase. Harvoni is a direct-acting antiviral (DAA) agent against the hepatitis C virus.

Harvoni Formulations

Tablet, Oral

- Harvoni: 90 mg of ledipasvir and 400 mg of sofosbuvir

Ribavirin Formulations:

- Capsule, Oral:
  - Rebetol: 200 mg
  - Ribasphere: 200 mg
  - Generic: 200 mg
- Solution, Oral:
  - Rebetol: 40 mg/mL (100 mL)
- Tablet, Oral:
  - Copegus: 200 mg
  - Moderiba (includes dose packs): 200 mg, 400 mg, 600 mg
  - Ribasphere: 200 mg, 400 mg, 600 mg
  - Ribasphere RibaPak (dose packs): 200 mg, 400 mg, 600 mg
  - Generic: 200 mg

FDA Approved Indications:

Harvoni is a fixed-dose combination of ledipasvir, a HCV NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor/oral tablet formulation, indicated with or without ribavirin for the treatment of chronic hepatitis C virus (HCV) in:

- Adults with genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis
- Adults with genotype 1 infection with decompensated cirrhosis, in combination with ribavirin
- Adults with genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with ribavirin
- Pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 1, 4, 5, or 6 without cirrhosis or with compensated cirrhosis

Appendices

Appendix A: Abbreviation Key

APRI: AST to platelet ratio
AASLD: American Association for the Study of Liver Diseases
CTP: Child Turcotte Pugh
FIB-4: Fibrosis-4 index
HCC: hepatocellular carcinoma

HCV: hepatitis C virus
IDSA: Infectious Diseases Society of America
MRE: magnetic resonance elastography
NS3/4A, NS5A/B: nonstructural protein
Peg-IFN: pegylated interferon
PI: protease inhibitor
RBV: ribavirin
RNA: ribonucleic acid

Appendix B: Approximate Scoring Equivalencies using METAVIR F3/F4 as Reference

Fibrosis/ Cirrhosis	Serologic Tests*				Radiologic Tests†		Liver Biopsy‡	
	Fibro Test	FIBRO Spect II	APRI	FIB-4	FibroScan (kPa)	MRE (kPa)	METAVIR	Ishak
Advanced fibrosis	≥0.59	≥42	>1.5	>3.25	≥9.5	≥4.11	F3	F4-5
Cirrhosis	≥0.75	≥42	>1.5	>3.25	≥12.0	≥4.71	F4	F5-6

*Serologic tests:
FibroTest (available through Quest as FibroTest or LabCorp as FibroSure)
FIBROSpect II (available through Prometheus Laboratory)
APRI (AST to platelet ratio index)
FIB-4 (Fibrosis-4 index: includes age, AST level, platelet count)
†Radiologic tests:
FibroScan (ultrasound-based elastography)
MRE (magnetic resonance elastography)
‡Liver biopsy (histologic scoring systems):
METAVIR F3/F4 is equivalent to Knodell, Scheuer, and Batts-Ludwig F3/F4 and Ishak F4-5/F5-6
METAVIR fibrosis stages: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = few septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis

Appendix C: 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			
Olysio				Simeprevir	
Sovaldi		Sofosbuvir			
Technivie*	Ombitasvir			Paritaprevir	Ritonavir
Viekira XR/PAK*	Ombitasvir		Dasabuvir	Paritaprevir	Ritonavir
Zepatier*	Elbasvir			Grazoprevir	

*Combination drugs
**Additional PIs no longer recommended: Victrelis (boceprevir), Incivek (telaprevir)

Appendix D: FDA-Approved Regimens and Treatment Durations
Adult Patients:

Treatment Naive/Experienced	Genotype	Failed Treatment Regimen	Recommended Regimen *See footnotes for duration*
No Cirrhosis			

Treatment Naive/Experienced	Genotype	Failed Treatment Regimen	Recommended Regimen *See footnotes for duration*
Treatment naive	1*	None	Harvoni^ *If pretreatment HCV RNA < 6 million IU/mL.*
	1*, 4	None	Harvoni + RBV§ *If post-liver transplantation.*
	1*, 4, 5, 6	None	Harvoni§
Treatment experienced	1*, 4	NS3 PI/Peg-IFN/RBV**	Harvoni + RBV§ *If post-liver transplantation.*
	1*, 4, 5, 6	NS3 PI/Peg-IFN/RBV**	Harvoni§
Compensated Cirrhosis (CTP/Child-Pugh Class A)			
Treatment naive	1*, 4	None	Harvoni + RBV§ *If post-liver transplantation.*
	1*, 4, 5, 6	None	Harvoni§
Treatment experienced	1*	NS3 PI/Peg-IFN/RBV**	Harvoni + RBV§
			Harvoni† *If RBV ineligible.*
	1*, 4	NS3 PI/Peg-IFN/RBV**	Harvoni + RBV§ *If post-liver transplantation.*
	4, 5, 6	NS3 PI/Peg-IFN/RBV**	Harvoni§
Decompensated Cirrhosis (CTP/Child-Pugh Class B or C)			
Treatment naive	1*, 4	None	Harvoni + RBV§
Treatment experienced	1*, 4	NS3 PI/Peg-IFN/RBV**	Harvoni + RBV§

*Subtype a or b, or unknown subtype
**NS3 includes Victrelis (boceprevir), Incivek (telaprevir) or Olysio (simeprevir)
^Treatment duration - 8 weeks
§Treatment duration - 12 weeks
†Treatment duration - 24 weeks

Pediatric Patients (≥12 years or ≥35 kg)

Treatment Naive/Experienced	Genotype	Failed Treatment Regimen	Recommended Regimen *See footnotes for duration*
No Cirrhosis			
Treatment naive	1*, 4, 5, 6	None	Harvoni§
Treatment experienced	1*, 4, 5, 6	Peg-IFN/RBV	Harvoni§
Compensated Cirrhosis (CTP/Child-Pugh Class A)			
Treatment naive	1*, 4, 5, 6	None	Harvoni§
Treatment experienced	1*	Peg-IFN/RBV	Harvoni† .
	4, 5, 6	Peg-IFN/RBV	Harvoni §

*Subtype a or b, or unknown subtype
§Treatment duration - 12 weeks
†Treatment duration - 24 weeks

Appendix E: AASLD-IDSA Recommended Regimens and Treatment Durations

Treatment Naive/Experienced	Genotype	Failed Treatment Regimen	Recommended Regimen *See footnotes for duration*
No cirrhosis			
Treatment naive	1*, 4	None	Harvoni + RBV§ *If liver transplant recipient.*
	1a, 1b, 4, 5, 6	None	Harvoni§
Treatment experienced	1*	Sovaldi/Peg-IFN/RBV	Harvoni + RBV§
		NS3 PI/Peg-IFN/RBV**	Harvoni§
	1*, 4	Not specified	Harvoni + RBV§ *If post-liver transplantation.*
	1a, 1b, 4, 5, 6	Peg-IFN/RBV	Harvoni§
Compensated cirrhosis (CTP/Child-Pugh Class A)			
Treatment naive	1*, 4	None	Harvoni + RBV§ *If post-liver transplantation.*
			Harvoni† *If post-liver transplantation and if RBV ineligible.*
	1a, 1b, 4, 5, 6	None	Harvoni§
Treatment experienced	1*	Sovaldi/Peg-IFN/RBV	Harvoni + RBV†
		NS3 PI/Peg-IFN/RBV**	Harvoni + RBV§
			Harvoni† *If RBV ineligible.*
	1*, 4	Not specified	Harvoni + RBV§ *If post-liver transplantation.*
	1a, 1b, 4	Peg-IFN/RBV	Harvoni + RBV§
		Peg-IFN/RBV	Harvoni† *If RBV ineligible.*
	5, 6	Peg-IFN/RBV	Harvoni§
Decompensated cirrhosis (CTP/Child-Pugh Class B or C)			
Treatment naive	1*, 4	Not specified	Harvoni + RBV§ *If post-liver transplantation.*
Treatment experienced	1*, 4	Sovaldi-based regimen	Harvoni + RBV†
		Not specified	Harvoni + RBV§ *If post-liver transplantation.*
Not specified	1*, 4	Not specified	Harvoni + RBV§
			Harvoni† *If RBV ineligible.*

*Any or unknown subtype
**NS3 includes Victrelis (boceprevir), Incivek (telaprevir) or Olysio (simprevir)
§Treatment duration - 12 weeks
†Treatment duration - 24 weeks

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
N/A	

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 D and E per AASLD guidelines and FDA-approved indications. The initial approval period is shortened to 8 weeks.	08/16	09/16
Added pediatric (≥12 years or ≥35 kg) indication expansion for GT 1,4,5,6. Removed positive response to therapy requirement per specialist feedback.	04/17	05/17

References

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12. Ribavirin (systemic): Drug information. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed July 11, 2016.

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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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.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.