Clinical Policy: Ledipasvir/Sofosbuvir (Harvoni)
Reference Number: HIM.PA.SP3
Effective Date: 08/16
Last Review Date: 08/17
Line of Business: Health Insurance Marketplace

Coding Implications
Revision Log

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

Description
Ledipasvir/sofosbuvir (Harvoni®) is a combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor.

FDA approved indication
Harvoni is indicated:
- For the treatment of HCV in adults with genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis
- For the treatment of HCV in adults with genotype 1 infection with decompensated cirrhosis, in combination with ribavirin
- For the treatment of HCV in adults with genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with ribavirin
- For the treatment of 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

Policy/Criteria
Provider must submit documentation (including office chart notes and lab results) supporting that member has met all approval criteria

I. Initial Approval Criteria

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

1. Diagnosis of chronic hepatitis C infection as evidenced by detectable HCV ribonucleic acid (RNA) levels over a six-month period;
2. Prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious disease specialist;
3. Age ≥ 12 years or body weight ≥ 35kg;
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 one of the following (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) - and the HCC 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 and b):
   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 and prescribed treatment duration is >12 weeks, member has contraindication or clinically significant adverse effects to Epclusa;
10. 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;
11. If prescribed with ribavirin, at time of request, member has none of the following contraindications:
    a. Pregnancy or possibility of pregnancy - member or partner;
    b. Coadministration with didanosine;
    c. Significant/unstable cardiac disease;
    d. Hemoglobinopathy (e.g., thalassemia major, sickle cell anemia);
    e. Hemoglobin < 8.5 g/dL;
    f. Creatinine clearance < 50 ml/min;
12. Dose does not exceed 90/400 mg/day (1 tablet/day).

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. Refer to HIM.PHAR.21 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Documentation of positive response to therapy;
3. Pharmacy claims support adherence to therapy;
4. If request is for a dose increase, new dose does not exceed 90/400 mg/day (1 tablet/day).

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

A. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via health plan benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 for specialty months (whichever is less); or
2. Refer to HIM.PA.21 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized)

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 – HIM.PHAR.21 or evidence of coverage documents

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

APRI: AST to platelet ratio
AASLD: American Association for the Study of Liver Diseases
CTP: Child Turcotte Pugh
FDA: Food and Drug Administration
FIB-4: Fibrosis-4 index
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
IDSA: Infectious Diseases Society of America
IV: intravenous
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	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†

Treatment Naive/Experienced	Genotype	Failed Treatment Regimen	Recommended Regimen *See footnotes for duration*
			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

V. 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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
New policy created. In relation to the current CP.PHAR.17 Hepatitis C Therapies policy, please note the following modifications or additions: • HCV RNA levels over six-month period added to confirm infection is chronic per AASLD guidelines. • Life expectancy "greater than or equal to 12 months if HCC and awaiting transplant" is modified to indicate "greater than or equal to 12 months with HCV therapy" per AASLD guidelines. • 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) per the AASLD HCC guidelines (guidelines are added to the reference section). In the regimen tables, HCC can fall under compensated or decompensated cirrhosis but not under "no cirrhosis" per section I criteria. • Methods to diagnose fibrosis/cirrhosis are modified to require presence of HCC, liver biopsy or a combination of one serologic and one radiologic test per AASLD guidelines. Serologic and radiologic tests are updated and correlated with METAVIR per Appendix B. Note that Hepascore has been discontinued and that both LabCorp and Quest offer FibroTest. FibroSpect II has been recently updated to correlate with METAVIR F3/F4 and is offered now by Prometheus rather than Quest. APRI and FIB-4 are calculations based on AST and platelets. • 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 to accommodate verification of HCV RNA status within that time - AASLD guidelines recommended testing at 4 and 6 weeks.	08/16	
Added pediatric (≥12 years or ≥35 kg) indication expansion for genotype 1,4,5,6. Updated contraindications. Allowed full therapy regimen at initial approval duration.	04/17	08/17

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.

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