Clinical Policy: ledipasvir-sofosbuvir (Harvoni)

Reference Number: NM.CP.PPA.04
Effective Date: 1/1/19
Last Review Date: 1/11/23
Revision Log

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

- 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

Black Box Warning
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.

Product Availability
Oral tablet
Generic: ledispasvir/sofosbuvir 90 mg/400 mg

Brand: (Harvoni) ledispasvir/sofosbuvir 90 mg/400 mg
(Harvoni) ledispasvir/sofosbuvir 45 mg/200 mg
Oral pellets
Brand: (Harvoni) ledispasvir/sofosbuvir 45 mg/200 mg
(Harvoni) ledispasvir/sofosbuvir 33.75 mg/150 mg

Policy/Criteria

It is the policy of Western Sky Community Care (WSCC) 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 will be approved for a maximum duration of 8 weeks (see appendices C and D)*

2. Confirmed HCV genotype is 1, 4, 5, or 6;
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 of at least 3 years
6. If age 18 or older, documented clinically appropriate reason for inability to use Mavyret or generic Epclusa;
7. Life expectancy ≥ 12 months with HCV treatment (this can be assumed unless otherwise stated);
8. ********Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see appendices C & D)*;
9. If used in combination with ribavirin, member has no absolute contraindications to ribavirin.
10. ********Dose as follows:
    a. **For Adults:** ledipasvir/sofosbuvir 90 mg/400 mg (1 tab) per day.(approve generic only)
    b. **For Pediatrics:**
        i. Body weight ≥35 kg: ledipasvir/sofosbuvir 90 mg/400 mg per day (approve generic only)
        ii. Body weight 17 kg to < 35 kg: ledipasvir/sofosbuvir 45 mg/200 mg per day
        Body weight < 17 kg: ledipasvir/sofosbuvir 33.75 mg/150 mg per day

Approval duration: up to a total of 24 weeks*
*(*Approved duration should be consistent with Appendix C &D)* ******If treatment regimen varies in dosing or interval from FDA or AASLD-IDSA guideline recommendations but it is documented on PA request/office chart notes that requested regimen in consultation with Project ECHO—please approve regimen.**

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.PMN.53 for Medicaid.

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 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;
ii. Confirmed HCV genotype is 1, 4, 5, or 6;

2. Member is responding positively to therapy;
3. ****Dose as follows:
   a. **For Adults:** ledipasvir/sofosbuvir 90 mg/400 mg (1 tab) per day.
   b. **For Pediatrics:**
      i. Body weight ≥35 kg: ledipasvir/sofosbuvir 90 mg/400 mg per day
      ii. Body weight 17 kg to < 35 kg: ledipasvir/sofosbuvir 45 mg/200 mg per day
      iii. Body weight < 17 kg: ledipasvir/sofosbuvir 33.75 mg/150 mg per day

Approval duration: up to a total of 24 weeks*
*(*Approved duration should be consistent with appendices C &D)* ****If treatment regimen varies in dosing or interval from FDA or AASLD-IDSA guideline recommendations but it is documented on PA request/office chart notes that requested regimen in consultation with Project ECHO—please approve regimen.**

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.PMN.53 for Medicaid.

Appendices

Appendix A: Abbreviation/Acronym Key

AASLD: American Association for the Study of Liver Diseases
APRI: AST to platelet ratio
FDA: Food and Drug Administration
FIB-4: Fibrosis-4 index
HBV: hepatitis B virus
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
HIV: human immunodeficiency virus
IDSA: Infectious Diseases Society of America
IQR: interquartile range
MRE: magnetic resonance elastography
NS3/4A, NS5A/B: nonstructural protein
PegIFN: pegylated interferon
RBV: ribavirin
RNA: ribonucleic acid

***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 (transient 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 B: 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

***Additional PIs no longer recommended that have been discontinued: Victrelis (boceprevir), Incivek (telaprevir)*

Appendix C:
Treatment duration for patients 3 years of age and older

Genotype	History	Treatment	Duration
1	Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Harvoni	12 wk*
	Treatment- experienced† **without cirrhosis**	Harvoni	12 wk
	Treatment- experienced† with compensated cirrhosis (Child-Pugh A)	Harvoni	24 wk‡
	Treatment-naïve and treatment-experienced† with decompensated cirrhosis (Child-Pugh B or C)	Harvoni + RBV	12 wk
1 or 4	Treatment-naïve and treatment-experienced† liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Pugh A)	Harvoni + RBV	12 wk
4, 5, 6	Treatment-naïve and treatment-experienced† without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Harvoni + RBV	12 wk

***** HARVONI for 8 weeks can be considered in treatment-naïve genotype 1 patients without cirrhosis who have pretreatment HCV RNA less than 6 million IU/mL [see Clinical Studies (14.2)].
† Treatment-experienced patients have failed a peginterferon alfa +/- ribavirin based regimen with or without an HCV protease inhibitor.
‡ HARVONI + ribavirin for 12 weeks can be considered in treatment-experienced genotype 1 patients with cirrhosis who are eligible for ribavirin

Appendix D: AASLD-IDSA Recommended Regimens and Treatment Durations
https://www.hcvguidelines.org/

Appendix E:
Any of the following meet the definition for cirrhosis per NM state directives:

- APRI >= 1.0
- Fib-4 >= 3.25
- Transient Elastography Score >= 12.5 dP3 (F4 equivalent)
- Fibrotest >= 0.73 (f4 equivalent) OR Fibrometer with F4 predominance
- Radiographic imaging or physical exam findings consistent with cirrhosis
- Liver biopsy confirming a METAVIR score of F4

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

	1 Point	2 Points	3 Points
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: Contraindications

- 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.

References

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Revision Log

Reviews, Revisions, and Approvals	Date	Approval Date
New clinical policy created for WSCC based on New Mexico requirements	11/18	11/18
Added provision for approval of drug dosing and interval (despite not meeting AASLD and IDSA recommended guidelines) if regimen is recommended/requested after consultation with Project ECHO; added Project ECHO to references; JJM	1/25/19	1/25/19
Renamed clinical policy per corporate guidelines; Changed from NM.CP.PHAR.04 to NM.CP.PPA.04; Name presented at WSCC P&T Committee;	3/20/19	3/20/19
Updated indications to include pediatric patients 3 years of age and older per new FDA indication from August 2019; Edited required materials that provider must submit to include various PA forms AND Uniform NM HCV Checklist; Removed need for contraindication to Mavyret; removed section in Appendix F which lists acceptable medical justification for inability to use Mavyret. Removed instruction to edit co-pay	9/9/19	

Reviews, Revisions, and Approvals	Date	Approval Date
to $0. Updated references. Removed “If denial is likely please make attempt to prescriber’s office for peer-to-peer”		
Updated indication for age 3 or older. Added weight based max dosing for pediatrics. Updated references.	10/16/19	
Approved by WSCC P&T Committee Meeting		10/23/19
Annual Review. References updated. Reviewed and approved by WSCC P&T Committee.	1/29/20	1/29/20
Edited criteria to match updated directive from NM HSD, MAD Supplement 20-13 to include updated forms. Updated references to reflect this change in NM Medicaid direction.	1/15/21	
Annual review. Added redirection to generic Epclusa or Mavyret for adults. Reviewed and approved by WSCC P&T Committee.		1/20/21
Updated references and links to NM HCV Uniform HCV checklist.	1/7/22	
Annual Review. Reviewed and approved by WSCC P&T Committee.		1/12/22
Updated dosing portion from “Dose does not exceed” to “Dosing as follows” to prevent underdosing for pediatric patients.	10/10/22	
Updated wording on dosage. Reviewed and approved by WSCC P&T Committee.		10/12/22
Annual Review. Updated References. Removed requirement for Drug Authorization Form and Uniform New Mexico HCV Checklist. Reviewed and approved by WSCC P&T Committee.	1/9/23	1/11/23