RXADVANCE
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Clinical Policy Title:	ledipasvir/sofosbuvir
Policy Number:	RxA.161
Drug(s) Applied:	Harvoni®
Original Policy Date:	02/07/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

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.

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.

Dosing Information

Drug Name	Indication	Dosing Regimen*,**	Maximum Dose
Ledipasvir/ Sofosbuvir (Harvoni®)	HCV Genotype 1	Pediatric (age 3+): Weight-based • <17 kg - Oral pellets: 33.75 mg ledipasvir/150 mg sofosbuvir once daily • 17 to <35 kg - Oral pellets, tablets: 45 mg ledipasvir/200 mg sofosbuvir once daily • ≥35 kg - Oral pellets, tablets: 90 mg ledipasvir/400 mg sofosbuvir once daily Adult (age 18+): • 1 tablet PO once daily Treatment duration: • Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh	Pediatric (age 3+): • <17 kg - Oral pellets: 33.75 mg ledipasvir/150 mg sofosbuvir once daily • 17 to <35 kg - Oral pellets, tablets: 45 mg ledipasvir/200 mg sofosbuvir once daily • ≥35 kg - Oral pellets, tablets: 90 mg ledipasvir/400 mg sofosbuvir once daily Adult: • 1 Oral tablet/day (sofosbuvir 400 mg/ ledipasvir 90 mg)

		A) whose HCV viral load is less than 6 million IU/mL: ○ For 8 weeks (12 weeks for black and/or HIV-coinfected patients) • Treatment-naïve with compensated cirrhosis: for 12 weeks • Treatment-experienced with PegIFN/RBV without cirrhosis: for 12 weeks • Treatment-experienced with compensated cirrhosis (Child-Pugh A): for 24 weeks • Treatment-naïve and treatment-experienced with decompensated cirrhosis (Child-Pugh B or C): for 12 weeks with RBV	
Ledipasvir/ Sofosbuvir (Harvoni®)	HCV Genotype 1 or 4	Pediatric (age 3+): Weight-based • <17 kg - Oral pellets: 33.75 mg ledipasvir/150 mg sofosbuvir once daily • 17 to <35 kg - Oral pellets, tablets: 45 mg ledipasvir/200 mg sofosbuvir once daily • ≥35 kg - Oral pellets, tablets: 90 mg ledipasvir/400 mg sofosbuvir once daily Adult (age 18+): • 1 tablet PO once daily Treatment Duration: • Treatment-naïve and treatment-experienced liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Pugh A): for 12 weeks with RBV	Pediatric: • <17 kg - Oral pellets: 33.75 mg ledipasvir/150 mg sofosbuvir once daily • 17 to <35 kg - Oral pellets, tablets: 45 mg ledipasvir/200 mg sofosbuvir once daily • ≥35 kg - Oral pellets, tablets: 90 mg ledipasvir/400 mg sofosbuvir once daily Adult: • 1 Oral tablet/day (sofosbuvir 400 mg/ ledipasvir 90 mg)
Ledipasvir/ Sofosbuvir (Harvoni®)	HCV Genotype 4, 5, or 6	Pediatric (age 3+): Weight-based • <17 kg - Oral pellets: 33.75 mg ledipasvir/150 mg sofosbuvir once daily • 17 to <35 kg - Oral pellets, tablets: 45 mg ledipasvir/200 mg sofosbuvir once daily • ≥35 kg - Oral pellets, tablets: 90 mg ledipasvir/400 mg sofosbuvir once daily Adult (age 18+): • 1 tablet PO once daily Treatment duration:	Pediatric: • <17 kg - Oral pellets: 33.75 mg ledipasvir/150 mg sofosbuvir once daily • 17 to <35 kg - Oral pellets, tablets: 45 mg ledipasvir/200 mg sofosbuvir once daily • ≥35 kg - Oral pellets, tablets: 90 mg ledipasvir/400 mg sofosbuvir once daily Adult:

		• Treatment-naïve and treatment-experienced without cirrhosis or with compensated cirrhosis (Child-Pugh A): for 12 weeks	• 1 Oral tablet/day (sofosbuvir 400 mg/ ledipasvir 90 mg)

**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.*
*** Treatment-experienced refers to previous treatment with peginterferon/RBV unless otherwise stated.*

Dosage Forms

- 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

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

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.
5. Age 3 years of age or older;
6. Member meets one of the following (a, 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. Life expectancy is 12 months or greater with HCV treatment;
8. Member meets one of the following (a or b):
   a. Age is less than 6 years of age;
   b. For ages 6 years or older, or weight 17 kg or greater, member meets one of the following (i or ii):
      i. Request is for 8 weeks of therapy only;
      ii. If request is for greater than 8 weeks of therapy, member must use one of the following (unless contraindicated or clinically significant adverse effects are experienced) (a or b):
         a) If age is between 6 and 11 years, or weight between 17 kg and 44 kg, member must use sofosbuvir/velpatasvir (Epclusa®) at up to maximally indicated doses;
         b) If age is 12 years or older, or weight is greater than 44 kg, member must use Mavyret® or sofosbuvir/velpatasvir (Epclusa®) at up to maximally indicated doses
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 Background for reference);
11. Dose does not exceed ledipasvir/sofosbuvir 90 mg/400 mg per day (1 tablet/day).

Approval Duration:
Commercial: Up to 24 weeks*
Medicaid: Up to 24 weeks*
*(*Approval duration must be consistent with FDA or AASLD/IDSA recommendations.)*

II. Continued Therapy Approval

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
   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 per day (1 tablet/day).

Approval Duration: Up to 24 weeks*
*(*Approved duration must be consistent with FDA or AASLD-IDSA recommendations.)*

III. Appendices

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
IDSA: Infectious Diseases Society of America
NS3/4A, NS5A/B: nonstructural protein
RBV: ribavirin
PegIFN: pegylated interferon

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	Maximum Dose
Epclusa® (sofosbuvir/ velpatasvir)	**HCV Genotype 1, 4, 5, or 6:** Without cirrhosis or with compensated cirrhosis, treatment-naïve or -experienced patient • 1 tablet PO once daily for 12 weeks With decompensated cirrhosis treatment-naïve or -experienced patient • 1 tablet PO once daily for 12 weeks AND RBV • If ineligible for RBV, then 1 tablet PO once daily for 24 weeks ǂ With decompensated cirrhosis in whom prior sofosbuvir- or NS5A-based treatment experienced failed • 1 tablet PO once daily for 24 weeks AND RBV **HCV Genotype 1b:** With compensated cirrhosis or without cirrhosis and non-NS5A inhibitor, sofosbuvir-containing regimen experienced • 1 tablet PO once daily for 12 weeks	1 tablet/day (sofosbuvir 400 mg/velpatasvir 100 mg)

Mavyret® (glecaprevir/ pibrentasvir)	**HCV Genotype 1, 4, 5, or 6:**
	Treatment-naive
	• Without cirrhosis:
	  ○ 3 tablets PO once daily for 8 weeks
	• With compensated cirrhosis:
	  ○ 3 tablets PO once daily for 12 weeks
	
	Treatment-experienced (with IFN/pegIFN + RBV)
	• Without cirrhosis:
	  ○ 3 tablets PO once daily for 8 weeks
	• With compensated cirrhosis
	  ○ 3 tablets PO once daily for 12 weeks
	
	HCV Genotype 1:
	Treatment-experienced with sofosbuvir
	• Without cirrhosis or with compensated cirrhosis:
	  ○ 3 tablets PO once daily for 12 weeks
	
	HCV Genotype 4, 5, or 6:
	Treatment-experienced with sofosbuvir
	• Without cirrhosis or with compensated cirrhosis:
	  ○ 3 tablets PO once daily for 12 weeks
		3 tablets/day (glecaprevir 300 mg/ pibrentasvir 120 mg)

Zepatier® (grazoprevir/ elbasvir)	**Genotype 1a:** Treatment-naïve or pegIFN/RBV-experienced with or without compensated cirrhosis WITHOUT baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93 • 1 tablet PO once daily for 12 weeks Treatment-naïve or PegIFN/RBV experienced with or without compensated cirrhosis WITH baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93 • 1 tablet PO once daily AND RBV for 16 weeks **Genotype 1b:** Treatment-naïve or PegIFN/RBV experienced with or without compensated cirrhosis • 1 tablet PO once daily for 12 weeks **Genotype 1a or 1b:** Treatment-experienced with or without compensated cirrhosis WITHOUT baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93 • 1 tablet PO once daily AND RBV for 12 weeks Treatment-experienced with or without compensated cirrhosis WITH baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93 • 1 tablet PO once daily AND RBV for 16 weeks **Genotype 4:** Treatment-naïve with or without compensated cirrhosis • 1 tablet PO once daily for 12 weeks Virologic relapse after prior pegIFN/RBV therapy: • 1 tablet PO once daily for 12 weeks Virologic failure while on pegIFN/RBV therapy: • One tablet PO once daily AND RBV for 16 weeks	1 tablet/day (grazoprevir 100 mg/ elbasvir 50 mg)

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*

‡ 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: General Information

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	

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

References

1. Harvoni Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; March 2020. Available at http://www.harvoni.com/. Accessed July 29, 2020.
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 July 29, 2020.
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.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Policy title table was updated. 2. Background was updated to include updates in indication. 3. Dosing information updated. 4. Dosage Forms section updated. 5. Therapeutic alternatives section updated. 6. Added age and weight-based criteria to initial approval criteria. 7. Updated initial approval duration. 8. Continued therapy criteria II.A.1 was rephrased to “Currently receiving medication that has been authorized by RxAdvance…”. 9. Updated abbreviations section. 10. QD was updated to "once daily" in document. 11. References were updated.	08/26/2020	12/07/2020