MEDICAL MUTUAL®

# Drug Policy

| Policy: | Harvoni® (sofosbuvir/ledipasvir) & sofosbuvir/ledipasvir authorized generics | Annual Review Date: 11/16/2023<br><br>Last Revised Date: 11/16/2023 |
|---|---|---|

## OVERVIEW

Harvoni is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, indicated for[1]:

- The treatment of chronic HCV genotype 1, 4, 5, and 6 infection in adults and pediatric patients ≥ 3 years of age with or without compensated cirrhosis; and
- Adult and pediatric patients ≥ 3 years of age with genotype 1 chronic HCV with decompensated cirrhosis in combination with ribavirin; and
- Adult and pediatric patients ≥ 3 years of age with genotype 1 or 4 chronic HCV who are liver transplant recipients with or without compensated cirrhosis, in combination with ribavirin.

## Dosing

In adults, the recommended dosage of ledipasvir/sofosbuvir is one tablet taken orally once daily with or without food.[1] The recommended dose of ledipasvir/sofosbuvir tablets or pellets in pediatric patients ≥ 3 years of age is based on weight. The ledipasvir/sofosbuvir pellets can be taken in pediatric patients who cannot swallow the tablet formulation. Table 1 below provides the recommended duration of therapy with ledipasvir/sofosbuvir. The ledipasvir/sofosbuvir authorized generic is only available as the 90 mg/400 mg strength tablet; ledipasvir/sofosbuvir is additionally available as a lower strength tablet (45 mg/200 mg) as well as oral pellets (45 mg/200 mg and 33.75 mg/150 mg).

**Table 1. Recommended Treatment Duration for Harvoni in Patients ≥ 3 Years of Age with Chronic HCV Genotype 1, 4, 5, or 6.[1]**

| Patient Population | Duration of Treatment |
|---|---|
| Genotype 1 – Treatment-naïve with or without compensated (Child Pugh A) cirrhosis | ledipasvir/sofosbuvir 12 weeks* |
| Genotype 1 – Treatment-experienced** without cirrhosis | ledipasvir/sofosbuvir 12 weeks |
| Genotype 1 – Treatment-experienced** with compensated (Child Pugh A) cirrhosis | ledipasvir/sofosbuvir 24 weeks† |
| Genotype 1 – Treatment-naïve and treatment-experienced** with decompensated (Child-Pugh B or C) cirrhosis. | ledipasvir/sofosbuvir + ribavirin‡ 12 weeks |
| Genotype 1 or 4 – Transplant recipients without cirrhosis, or with compensated (Child-Pugh A) cirrhosis | ledipasvir/sofosbuvir + ribavirin§ 12 weeks |
| Genotype 4, 5, or 6 – Treatment-naïve and treatment-experienced**, with or without compensated (Child-Pugh A) cirrhosis | ledipasvir/sofosbuvir 12 weeks |

Hepatitis C virus – Hepatitis C virus; * Harvoni for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pretreatment HCV RNA < 6 million IU/mL; ** Treatment-experienced patients who have failed treatment with either peginterferon alfa + ribavirin or a hepatitis C

virus protease inhibitor + peginterferon + ribavirin; † Harvoni for 12 weeks can be considered in treatment-experienced patients with cirrhosis who are eligible for ribavirin. The daily dose of ribavirin is weight-based (1,000 mg for patients < 75 kg and 1,200 mg for those ≥ 75 kg) administered in two divided doses. ‡ In patients with decompensated cirrhosis, the starting dosage of ribavirin is 600 mg and can be titrated up to 1,000 mg for patients <75 kg and 1,200 mg for those ≥75 kg in two divided doses with food. If the starting dosage of ribavirin is not well tolerated, the dosage should be reduced as clinically indicated based on hemoglobin levels. § The daily dosage of ribavirin is weight-based (1,000 mg for patients < 75 kg and 1,200 mg for those ≥ 75 kg) administered orally in two divided doses with food.

## Guidelines

For the most up-to-date guideline information always refer to the American Association for the Study of Liver Diseases (AASLD) guidelines. Ledipasvir/sofosbuvir is recommended in the circumstances outlined in Table 2.

**Table 2. AASLD Recommendations for Harvoni.[2]**

| DAA | Duration | FDA Approved (Y/N) | AASLD Level of Evidence |
|---|---|---|---|
| **Genotype 1, 4, 5, and 6 Chronic HCV Treatment-Naïve Adults – Recommended** | | | |
| ledipasvir/sofosbuvir | 12 weeks (± compensated cirrhosis)<br>Not recommended for genotype 6e if subtype is known. | Y | Class I, Level A<br>Class IIa, Level B (Genotype 4 compensated cirrhosis, Genotype 5/6 ± compensated cirrhosis) |
| ledipasvir/sofosbuvir | 8 weeks (HIV-uninfected, HCV RNA < 6 million IU/mL, no cirrhosis, absence of genotype 4r) | Y | Class I, Level B |
| **Genotype 1, 4, 5, and 6 Chronic HCV Pegylated Interferon/Ribavirin Treatment-Experienced Adults – Recommended** | | | |
| ledipasvir/sofosbuvir | 12 weeks (no cirrhosis) | Y | Class I, Level A (Genotype 1)<br>Class IIa, Level B (Genotype 4, 5, 6) |
| ledipasvir/sofosbuvir | 12 weeks (compensated cirrhosis) | Y | Class IIa, Level B (Genotype 5/6) |
| **Genotype 1 and 4 Chronic HCV Pegylated Interferon/Ribavirin Treatment-Experienced Adults – Alternative** | | | |
| ledipasvir/sofosbuvir + WBR | 12 weeks (compensated cirrhosis) | Y (Genotype 1)<br>N (Genotype 4) | Class I, Level A (Genotype 1)<br>Class IIa, Level B (Genotype 4) |
| **Genotype 1 Chronic HCV NS3/4A + Pegylated Interferon/Ribavirin Treatment-Experienced Adults – Recommended** | | | |
| ledipasvir/sofosbuvir | 12 weeks (no cirrhosis) | Y | Class I, Level A |
| **Genotype 1 Chronic HCV NS3/4A + Pegylated Interferon/Ribavirin Treatment-Experienced Adults – Alternative** | | | |
| ledipasvir/sofosbuvir + WBR | 12 weeks (compensated cirrhosis) | Y | Class I, Level A |
| **Genotype 1 Chronic HCV Non-NS5A Sovaldi-Containing Treatment-Experienced Adults – Alternative** | | | |
| ledipasvir/sofosbuvir + WBR | 12 weeks (no cirrhosis) | N | Class IIa, Level B |
| **Genotype 1, 4, 5, or 6 Chronic HCV, Decompensated Cirrhosis Adults Ribavirin Eligible – Recommended** | | | |
| ledipasvir/sofosbuvir + ribavirin | 12 weeks | Y | Class I, Level A |
| **Genotype 1, 4, 5, or 6 Chronic HCV, Decompensated Cirrhosis Adults Ribavirin Ineligible – Recommended** | | | |
| ledipasvir/sofosbuvir | 24 weeks | N | Class I, Level A |
| **Genotype 1, 4, 5, or 6 Chronic HCV, Decompensated Cirrhosis Adults Prior Sovaldi-Based Failure or NSA Failure – Recommended** | | | |

| | | | |
|---|---|---|---|
| ledipasvir/sofosbuvir + ribavirin | 24 weeks | N | Class II, Level C |
| **Genotype 1, 4, 5, or 6 Recurrent HCV Post-Liver Transplant, No Cirrhosis, Treatment-Naïve or Treatment-Experienced – Recommended** | | | |
| ledipasvir/sofosbuvir + WBR | 12 weeks | Y | Class I, Level B |
| **Genotype 1, 4, 5, or 6 Recurrent HCV Post-Liver Transplant, Compensated Cirrhosis, Treatment-Naïve or Treatment-Experienced – Recommended** | | | |
| ledipasvir/sofosbuvir + WBR | 12 weeks | Y | Class I, Level A |
| **Genotype 1, 4, 5, or 6 Recurrent HCV Post-Liver Transplant, Decompensated Cirrhosis, Treatment-Naïve or Treatment-Experienced – Recommended** | | | |
| ledipasvir/sofosbuvir + ribavirin | 12 to 24 weeks | Y | Class I, Level B |
| **Genotype 1, 4, 5, or 6 Organ Recipients from HCV RNA-Positive Donors, Adults – Recommended** | | | |
| ledipasvir/sofosbuvir | 12 weeks | N | Class I, Level C |

**Table 2 (continued). AASLD Recommendations for Harvoni.[2]**

| DAA | Duration | FDA Approved (Y/N) | AASLD Level of Evidence |
|---|---|---|---|
| **Genotype 1, 4, 5, or 6 Kidney Transplant Treatment-Naïve or DAA-Experienced ± Compensated Cirrhosis, Adults – Recommended** | | | |
| ledipasvir/sofosbuvir | 12 weeks | N | Class I, Level A |
| **Genotype 1, 4, 5, or 6 Treatment-Naïve Adolescents ≥ 3 years, ± Compensated Cirrhosis – Recommended** | | | |
| ledipasvir/sofosbuvir | 12 weeks | Y | Class I, Level B |
| **Genotype 1, 4, 5, or 6 Treatment-Experienced Adolescents ≥ 3 years, ± Compensated Cirrhosis – Recommended** | | | |
| ledipasvir/sofosbuvir | 12 weeks (GT1 no cirrhosis) | Y | Class I, Level C |
| ledipasvir/sofosbuvir | 24 weeks (GT1 compensated cirrhosis) | Y | Class I, Level C |
| ledipasvir/sofosbuvir | 12 weeks (GT 4, 5, or 6 ± compensated cirrhosis) | Y | Class I, Level C |

AASLD – American Association for the Study of Liver Diseases; DAA – Direct-acting antiviral; Y – Yes; N – No; HCV – Hepatitis C virus; HIV – Human immunodeficiency virus.

*****UPDATED TABLE*****

**Table 2. AASLD Recommendations for Harvoni.[2]**

| DAA | Duration | FDA Approved (Y/N) | AASLD Level of Evidence |
|---|---|---|---|
| **Genotype 1, 4, 5, and 6 Chronic HCV Treatment-Naïve Adults – Recommended** | | | |
| ledipasvir/sofosbuvir | 12 weeks (± compensated cirrhosis)<br>Not recommended for genotype 6e if subtype is known. | Y | Class I, Level A<br>Class IIa, Level B (Genotype 4 compensated cirrhosis, Genotype 5/6 ± compensated cirrhosis) |
| ledipasvir/sofosbuvir | 8 weeks (HIV-uninfected, HCV RNA < 6 million IU/mL, no cirrhosis, absence of genotype 4r) | Y | Class I, Level B |

| | | | |
|---|---|---|---|
| **Genotype 1, 4, 5, or 6 Chronic HCV, Decompensated Cirrhosis Adults Ribavirin Eligible – Recommended** | | | |
| ledipasvir/sofosbuvir + ribavirin | 12 weeks | Y | Class I, Level A |
| **Genotype 1, 4, 5, or 6 Chronic HCV, Decompensated Cirrhosis Adults Ribavirin Ineligible – Recommended** | | | |
| ledipasvir/sofosbuvir | 24 weeks | N | Class I, Level A |
| **Genotype 1, 4, 5, or 6 Chronic HCV, Decompensated Cirrhosis Adults Prior Sovaldi or NSA Failure – Recommended** | | | |
| ledipasvir/sofosbuvir + ribavirin | 24 weeks | N | Class II, Level C |
| **Genotype 1, 4, 5, or 6 Recurrent HCV Post-Liver Transplant, No Cirrhosis, Treatment-Naïve or Treatment-Experienced – Recommended** | | | |
| ledipasvir/sofosbuvir | 12 weeks | Y | Class I, Level B |
| **Genotype 1, 4, 5, or 6 Recurrent HCV Post-Liver Transplant, Compensated Cirrhosis, Treatment-Naïve or Treatment-Experienced – Recommended** | | | |
| ledipasvir/sofosbuvir | 12 weeks | Y | Class I, Level A |
| **Genotype 1, 4, 5, or 6 Recurrent HCV Post-Liver Transplant, Decompensated Cirrhosis, Treatment-Naïve or Treatment-Experienced – Recommended** | | | |
| ledipasvir/sofosbuvir + ribavirin | 12 to 24 weeks | Y | Class I, Level B |
| **Genotype 1, 4, 5, or 6 Kidney Transplant Treatment-Naïve or DAA-Experienced ± Compensated Cirrhosis, Adults – Recommended** | | | |
| ledipasvir/sofosbuvir | 12 weeks | N | Class I, Level A |
| **Genotype 1, 4, 5, or 6 Treatment-Naïve Adolescents ≥ 3 years, ± Compensated Cirrhosis – Recommended** | | | |
| ledipasvir/sofosbuvir | 12 weeks | Y | Class I, Level B |

**Table 2 (continued). AASLD Recommendations for Harvoni.[2]**

| DAA | Duration | FDA Approved (Y/N) | AASLD Level of Evidence |
|---|---|---|---|
| **Genotype 1, 4, 5, or 6 Treatment-Experienced (Interferon + Protease Inhibitor) Adolescents ≥ 3 years, ± Compensated Cirrhosis – Recommended** | | | |
| ledipasvir/sofosbuvir | 12 weeks (GT1 no cirrhosis) | Y | Class I, Level C |
| ledipasvir/sofosbuvir | 24 weeks (GT1 compensated cirrhosis) | Y | Class I, Level C |
| ledipasvir/sofosbuvir | 12 weeks (GT 4, 5, or 6 ± compensated cirrhosis) | Y | Class I, Level C |

AASLD – American Association for the Study of Liver Diseases; DAA – Direct-acting antiviral; Y – Yes; N – No; HCV – Hepatitis C virus; HIV – Human immunodeficiency virus.

## POLICY STATEMENT

This policy involves the use of ledipasvir/sofosbuvir. Prior authorization is recommended for pharmacy benefit coverage of ledipasvir/sofosbuvir. Criteria are based on the guidance issued by American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA)/International Antiviral Society-USA (IAS-USA), prescribing information, clinical data, and expert review. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with ledipasvir/sofosbuvir as well as the monitoring required for adverse events and long-term efficacy, initial approval requires ledipasvir/sofosbuvir be prescribed by or in consultation with a physician who specializes in the condition being treated. ledipasvir/sofosbuvir is subject to the Hepatitis C Virus Direct-Acting Antivirals Preferred Specialty Management Policy.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of ledipasvir/sofosbuvir is recommended in those who meet the following criteria:

1. **Chronic Hepatitis C Virus (HCV) Genotype 1.** Approve for the duration noted if the patient meets all of the following criteria (A, B, and C):
   - **A)** Patient is ≥ 3 years of age; AND
   - **B)** Patient meets ONE of the following criteria (i, ii or iii):
     - **i.** Approve for 8 weeks if the patient meets all of the following criteria (a, b, c, d, and e):
       - **a)** Patient is treatment-naïve; AND
       - **b)** Patient does not have cirrhosis; AND
       - **c)** Patient does not have human immunodeficiency virus (HIV)[2] (patients with HIV should be reviewed the same as patients without HIV using *Criteria ii or iii below*); AND
       - **d)** Patient is not awaiting liver transplantation (patients awaiting liver transplantation should be reviewed using *Criteria ii or iii below*); AND
       - **e)** Baseline hepatitis C virus (HCV) RNA is < 6 million IU/mL; OR

**ii.** Approve for 12 weeks if the patient meets ONE the following criteria (a, b, or c):
- **a)** Patient is treatment-naïve AND does not meet criterion *Bi* above; OR
  Note: Treatment-naïve includes patients with or without HIV who are treatment-naïve with compensated [Child-Pugh A] cirrhosis regardless of baseline HCV RNA, or treatment-naïve patients with or without HIV without cirrhosis and baseline HCV RNA ≥ 6 million IU/mL. This would also include treatment-naïve patients awaiting transplant with compensated [Child-Pugh A] cirrhosis regardless of baseline HCV RNA or treatment-naïve patients awaiting transplant without cirrhosis and baseline HCV RNA ≥ 6 million IU/mL).
- **b)** Patient has previously been treated for hepatitis C virus (HCV) and does not have cirrhosis; OR
  Note: For patients with compensated cirrhosis [Child-Pugh A] see criterion *Biii* below, for patients with decompensated cirrhosis [Child-Pugh B or C] see criterion *Biic* below.
- **c)** Patient is treatment-naïve or has previously been treated for hepatitis C virus (HCV) and meets all of the following criteria ([1], [2], and [3]):
  - **(1)** Patient has decompensated (Child-Pugh B or C) cirrhosis; AND
  - **(2)** Patient is ribavirin eligible; AND
    Note: For ribavirin ineligible patients with decompensated cirrhosis, see criterion *Biiib* below
  - **(3)** Harvoni (brand or generic) will be prescribed in combination with ribavirin; OR

**iii.** Approve for 24 weeks in patients who meet ONE of the following (a or b):
- **(1)** Patient has previously been treated for hepatitis C virus (HCV) and has compensated (Child-Pugh A) cirrhosis; OR
- **(2)** Patient is treatment-naïve or has previously been treated for hepatitis C virus (HCV) and the patient meets both of the following criteria ([1] and [2]):
  - **a.** Patient has decompensated (Child-Pugh B or C) cirrhosis; AND
  - **b.** Patient is ribavirin ineligible, according to the prescriber; AND

**C)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

2. **Chronic Hepatitis C Virus (HCV) – Genotype 4, 5, OR 6.** Approve for 12 weeks if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 3 years of age; AND
   - **B)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

3. **Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotypes 1 OR 4.** Approve for 12 weeks if the patient meets the following criteria (A, B, C and D):
   - **A)** Patient is ≥ 3 years of age; AND
   - **B)** Patient has recurrent hepatitis C virus (HCV) after a liver transplantation; AND
   - **C)** The medication will be prescribed in combination with ribavirin; AND

**D)** The medication is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center[2]: a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

**Other Uses with Supportive Evidence**

4. **Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotypes 5 OR 6**. Approve for 12 weeks if the patient meets the following criteria (A, B, C and D):
   **A)** Patient is ≥ 18 years of age; AND
   **B)** Patient has recurrent hepatitis C virus (HCV) after a liver transplantation; AND
   **C)** The medication will be prescribed in combination with ribavirin; AND
   **D)** The medication is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center[2]: a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

5. **Hepatitis C Virus (HCV) Kidney Transplant Recipients, Genotype 1 or 4.** Approve for 12 weeks if the patient meets the following criteria (A, B, and C):
   **A)** Patient is ≥ 18 years of age; AND
   **B)** Patient is a kidney transplant recipient with hepatitis C virus (HCV); AND
   **C)** The medication is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center[2]: a gastroenterologist, hepatologist, infectious diseases physician, nephrologist, liver transplant physician, or a renal transplant physician.

6. **Patient Has Been Started on Harvoni (brand or generic).** Approve ledipasvir/sofosbuvir for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Approve the duration described above to complete a course of therapy (e.g., a patient who should receive 12 weeks, and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

**Approval.** See above criteria.

**CONDITIONS NOT RECOMMENDED FOR APPROVAL**

Harvoni has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. **Hepatitis C Virus (HCV) [any genotype], Combination with Any Other Direct-Acting Antivirals (DAAs) Not Including Ribavirin.** ledipasvir/sofosbuvir provides a complete antiviral regimen for patients

with genotype 1 HCV. Ledipasvir/sofosbuvir is not recommended to be used with other products containing sofosbuvir.

2. **Life Expectancy Less Than 12 Months Due to Non-Liver Related Comorbidities.** Patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis do not require treatment.[2] According to AASLD guidance, the panel recommends treatment for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence.

3. **Pediatric Patients (Age < 3 years).** The safety and efficacy of ledipasvir/sofosbuvir have not been established in pediatric patients < 3 years of age.[1]

4. **Retreatment with ledipasvir/sofosbuvir in Patients Who Have Previously Received ledipasvir/sofosbuvir (e.g., retreatment in prior null responders, prior partial responders, prior relapse patients, patients who have not completed a course of therapy due to an adverse reaction or for other reasons)**. There are other direct-acting antivirals indicated for patients who have previously been treated with ledipasvir/sofosbuvir.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

**Documentation Requirements:**
The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

## REFERENCES

1. Harvoni® tablets and oral pellets [prescribing information]. Foster City, CA: Gilead; March 2020.
2. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Updated November 6, 2019. Accessed on August 18, 2020.
3. Charlton M, Everson GT, Flamm SL, et al; for the SOLAR-1 Investigators. *Gastroenterology*. 2015;149:649-659.
4. Naggie, Cooper C, Saag M, et al; for the ION-4 Investigators. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. *N Engl J Med*. 2015;373:705-713.

**5.** Bourliere M, Bronowicki JP, de Ledinghen V, et al. Ledipasvir+sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomized, double-blind, phase 2 trial (SIRIUS). *Lancet Infect Dis.* 2015; 15:397-404.
**6.** Balistreri WF, Murray KF, Rosenthal P, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12 to 17 years old with hepatitis C virus genotype 1 infection. *Hepatology*. 2017;66(2):371-378.
**7.** Data on file. Gilead, Foster City CA. April 10, 2017.