Harvoni (sofosbuvir/ledipasvir)

Override(s)	Approval Duration
Prior Authorization Quantity Limit	Based on Genotype, Treatment status, Baseline HCV RNA status, Cirrhosis status, Transplant status, or Ribavirin Eligibility status

Medication	Quantity Limit
Harvoni (sofosbuvir/ledipasvir) 90 mg/400 mg tablets	1 tablet per day
Harvoni (ledipasvir/sofosbuvir) 45 mg/200 mg tablets	2 tablets per day
Harvoni (ledipasvir/sofosbuvir) 45 mg/200 mg pellets	2 packets of pellets per day
Harvoni (ledipasvir/sofosbuvir) 33.75 mg/150 mg pellets	1 packet of pellets per day

APPROVAL DURATION

Genotype and Status (HCV mono-infected or HCV/HIV-1 co-infected[a])	Associated Treatment Regimens	Total Approval Duration of Harvoni
Genotype 1 (treatment-naïve, baseline HCV RNA level of less than 6 million IU/mL, without cirrhosis)	Harvoni	8 or 12 [Δ] weeks
Genotype 1 (treatment-naïve, baseline HCV RNA level of greater than or equal to 6 million IU/mL, without cirrhosis)	Harvoni	12 weeks
Genotype 1 (treatment-naïve, with compensated cirrhosis)	Harvoni	12 weeks
Genotype 1 (dual P/R[2b] or triple[2d] treatment-experienced, without cirrhosis)	Harvoni	12 weeks
Genotype 1 (dual P/R[2b] or triple[2d] treatment-experienced with compensated cirrhosis)	Harvoni + RBV	12 weeks
Genotype 1 (dual P/R[2b] or triple[2d] treatment-experienced with compensated cirrhosis, ineligible for ribavirin)	Harvoni	24 weeks
Genotype 4, 5, or 6 (treatment-naïve, dual P/R[2b] or triple[2d] treatment experienced, with compensated cirrhosis or without cirrhosis)	Harvoni	12 weeks

Genotype 1 or4 (treatment-naïve or treatment-experienced, post-liver allograft transplant, with compensated cirrhosis or without cirrhosis)	Harvoni ± RBV[b]	12 weeks
Genotype 5 or 6 (treatment-naïve or treatment-experienced, post-liver allograft transplant, with compensated cirrhosis or without cirrhosis)	Harvoni	12 weeks
Genotype 1, 4, 5, or 6 (treatment-naïve, post-liver allograft transplant, with decompensated cirrhosis)	Harvoni + RBV	12 weeks
Genotype 1, 4, 5, or 6 (treatment-experienced, post-liver allograft transplant, with decompensated cirrhosis)	Harvoni + RBV	24 weeks
Genotypes 1, 4, 5 or 6 (treatment-naïve or dual P/R[2b] treatment-experienced, post-kidney transplant recipient, with compensated cirrhosis or without cirrhosis)	Harvoni	12 weeks
Genotype 1, 4, 5 or 6 (treatment naïve, or treatment-experienced, without sofosbuvir or NS5A[2a] with decompensated cirrhosis)	Harvoni + RBV	12 weeks
Genotype 1, 4, 5 or 6 (treatment-naïve or treatment-experienced without sofosbuvir or NS5A2a, ribavirin ineligible, with decompensated cirrhosis)	Harvoni	24 weeks
Genotype 1, 4, 5 or 6 (treatment-experienced with sofosbuvir-containing regimen, with decompensated cirrhosis)	Harvoni + RBV	24 weeks

[Δ]The September 2017 AASLD/IDSA treatment guidance recommends a 12 week course of therapy for certain subpopulations, such as individuals co-infected with HCV/HIV and African American individuals.

APPROVAL CRITERIA

Requests for Harvoni or authorized generic Harvoni (ledipasvir/sofosbuvir) may be approved if the following criteria are met:

I. Documentation is provided for a diagnosis of chronic hepatitis C (CHC) infection[a], which includes genotype and a positive HCV RNA result (AASLD/IDSA 2017, CDC 2013); **AND**;
II. Individual has received baseline evaluation for liver fibrosis to guide appropriate therapy; **AND**
III. If an 8 week treatment duration is requested, a copy of the baseline quantitative hepatitis C virus (HCV) RNA test result is provided to document baseline level of viremia; **AND**

IV. Individual does not have a short life expectancy (less than 12 months owing to non-liver related comorbid conditions) that cannot be remediated by treating HCV, by transplantation or other directed therapy (AASLD/IDSA 2017); **AND**

V. Individual has compensated[1] liver disease (with or without cirrhosis) or decompensated[1] liver disease;

AND

VI. Individual has had a prior trial (medication samples/coupons/discount cards are excluded from consideration as a trial) and inadequate response to brand Epclusa (sofosbuvir/velpatasvir), unless one of the following conditions apply:

A. Individual is using in **one** of the following antiviral treatment regimens (Label, AASLD/IDSA 2021):

1. Individual is 3 years of age or older; **AND**
2. As monotherapy for **one** of the following:
   a. Individual is treatment-naïve with compensated[1] cirrhosis or without cirrhosis and Genotype 1; **OR**
   b. Individual is dual P/R[2b] or triple[2d] treatment-experienced, with compensated[1] cirrhosis or without cirrhosis and Genotype1;

   AND

   c. Individual meets one of the following criteria:
      i. Prior trial of brand Epclusa (sofosbuvir/velpatasvir) with documented hypersensitivity, as manifested by a severe allergic reaction to any ingredient which is not also in Harvoni; **OR**
      ii. Individual is currently on and completing a course of therapy with the requested regimen; **OR**
      iii. Individual is concurrently using an agent that cannot be substituted with another agent or temporarily discontinued and is contraindicated or not recommended for concomitant use with the preferred regimen or regimens; **OR**
      iv. Individual is 3 to 5 years of age;

   OR

   d. Individual is treatment-naïve or dual P/R[2b] treatment-experienced, with compensated[1] cirrhosis or without cirrhosis and Genotype 4, 5 or 6; **AND**
   e. Individual meets one of the following criteria:
      i. Prior trial of brand Epclusa (sofosbuvir/velpatasvir) with documented hypersensitivity, as manifested by a severe allergic reaction to any ingredient which is not also in Harvoni; **OR**
      ii. Individual is currently on and completing a course of therapy with the requested regimen; **OR**
      iii. Individual is concurrently using an agent that cannot be substituted with another agent or temporarily discontinued and is contraindicated or not recommended for concomitant use with the preferred regimen or regimens; **OR**
      iv. Individual is 3 to 5 years of age;

OR

f. Individual is triple[2d] treatment-experienced, with compensated[1] cirrhosis or without cirrhosis and Genotype 4, 5 or 6; **AND**
g. Individual meets one of the following criteria:
    i. Prior trial of brand Epclusa (sofosbuvir/velpatasvir) with documented hypersensitivity, as manifested by a severe allergic reaction to any ingredient which is not also in Harvoni; **OR**
    ii. Individual is currently on and completing a course of therapy with the requested regimen; **OR**
    iii. Individual is concurrently using an agent that cannot be substituted with another agent or temporarily discontinued and is contraindicated or not recommended for concomitant use with the preferred regimen or regimens;
    iv. Individual is 3 to 5 years of age;

OR

h. Individual is treatment-naïve or treatment-experienced without a sofosbuvir or NS5A[2a]-containing regimen, ribavirin ineligible, with decompensated[1] cirrhosis and Genotypes 1, 4, 5 or 6; **AND**
i. Individual meets one of the following criteria:
    i. Prior trial of brand Epclusa (sofosbuvir/velpatasvir) with documented hypersensitivity, as manifested by a severe allergic reaction to any ingredient which is not also in Harvoni; **OR**
    ii. Individual is currently on and completing a course of therapy with the requested regimen; **OR**
    iii. Individual is concurrently using an agent that cannot be substituted with another agent or temporarily discontinued and is contraindicated or not recommended for concomitant use with the preferred regimen or regimens;
    iv. Individual is 3 to 17 years of age.

OR

j. Individual is a post-kidney transplant recipient, treatment-naïve or dual P/R[2b] treatment-experienced, with compensated[1] cirrhosis or without cirrhosis, and Genotypes 1, 4, 5, or 6;

OR

k. Individual is a post-liver allograft transplant recipient, treatment naïve or experienced, with compensated cirrhosis or without cirrhosis[b], and Genotype 1, 4, 5, or 6; **AND**
l. Individual meets one of the following criteria:
    i. Prior trial of brand Epclusa (sofosbuvir/velpatasvir) with documented hypersensitivity, as manifested by a severe allergic reaction to any ingredient which is not also in Harvoni; **OR**
    ii. Individual is currently on and completing a course of therapy with the requested regimen; **OR**
    iii. Individual is concurrently using an agent that cannot be substituted with another agent or temporarily discontinued and is contraindicated

or not recommended for concomitant use with the preferred regimen or regimens;

iv. Individual is 3 to 17 years of age;

OR

3. Individual is 3 years of age or older; **AND**
4. In combination with ribavirin for **one** of the following:
   a. Individual is dual P/R[2b] or triple[2d] treatment-experienced with compensated[1] cirrhosis, and Genotype 1; **AND**
   b. Individual meets one of the following criteria:
      i. Prior trial of brand Epclusa (sofosbuvir/velpatasvir) with documented hypersensitivity, as manifested by a severe allergic reaction to any ingredient which is not also in Harvoni; **OR**
      ii. Individual is currently on and completing a course of therapy with the requested regimen; **OR**
      iii. Individual is concurrently using an agent that cannot be substituted with another agent or temporarily discontinued and is contraindicated or not recommended for concomitant use with the preferred regimen or regimens; **OR**
      iv. Individual is 3 to 5 years of age

   OR

   c. Individual is treatment-naïve, or treatment-experienced with decompensated[1] cirrhosis and Genotypes 1, 4, 5 or 6; **AND**
   d. Individual meets one of the following criteria:
      i. Prior trial of brand Epclusa (sofosbuvir/velpatasvir) with documented hypersensitivity, as manifested by a severe allergic reaction to any ingredient which is not also in Harvoni; OR
      ii. Individual is currently on and completing a course of therapy with the requested regimen; **OR**
      iii. Individual is concurrently using an agent that cannot be substituted with another agent or temporarily discontinued and is contraindicated or not recommended for concomitant use with the preferred regimen or regimens; **OR**
      iv. Individual is 3 to 5 years of age

   OR

   e. Individual is a post-liver allograft transplant recipient, with compensated[1] cirrhosis, or without cirrhosis, and Genotypes 1 or 4; **AND**
   f. Individual meets one of the following criteria:
      i. Prior trial of brand Epclusa (sofosbuvir/velpatasvir) with documented hypersensitivity, as manifested by a severe allergic reaction to any ingredient which is not also in Harvoni; **OR**
      ii. Individual is currently on and completing a course of therapy with the requested regimen; **OR**
      iii. Individual is concurrently using an agent that cannot be substituted with another agent or temporarily discontinued and is contraindicated

or not recommended for concomitant use with the preferred regimen or regimens;

iv. Individual is 3 to 17 years of age;

OR

g. Individual is a post-liver allograft transplant recipient, decompensated[1] cirrhosis, and Genotypes 1, 4, 5 or 6; **AND**
h. Individual meets one of the following criteria:
    i. Prior trial of brand Epclusa (sofosbuvir/velpatasvir) with documented hypersensitivity, as manifested by a severe allergic reaction to any ingredient which is not also in Harvoni; **OR**
    ii. Individual is currently on and completing a course of therapy with the requested regimen; **OR**
    iii. Individual is concurrently using an agent that cannot be substituted with another agent or temporarily discontinued and is contraindicated or not recommended for concomitant use with the preferred regimen or regimens; **OR**
    iv. Individual is 3 to 17 years of age.

Harvoni (ledipasvir/sofosbuvir) may not be approved for the following:

I. Individual is requesting in concurrent therapy with contraindicated or not recommended agents, including but not limited to the following: amiodarone, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, elvitegravir/cobicistat/emtricitabine/tenofovir DF, tipranavir/ritonavir, rosuvastatin or p-gp inducers (including but not limited to rifabutin, rifampin, rifapentine, St John's Wort); **OR**
II. Individual is using in combination with a regimen containing a non-nucleoside NS5B polymerase inhibitor (such as dasabuvir) or another nucleotide NS5B polymerase inhibitor (such as sofosbuvir); **OR**
III. Individual is using in combination with a regimen containing another NS5A[2a]; **OR**
IV. Individual is using in combination with a regimen containing a NS3/4A[2c] protease inhibitor; **OR**
V. Individual is requesting the regimen for re-treatment and either failed to achieve a SVR (defined as a lower limit HCV RNA of 25 IU/mL) or relapsed after achieving a SVR during a prior successfully completed treatment regimen consisting of a NS5A[2a] inhibitor.

Notes:

[a]Per label and AASLD/IDSA treatment guidance, Harvoni (ledipasvir/sofosbuvir) may be used in individuals who are co-infected with HIV-1. The AASLD/IDSA treatment guidance recommends that concurrent use with tenofovir disoproxil fumarate (TDF) should be avoided with an eGFR below 60 mL/min.

[b]While the label recommends the addition of ribavirin for liver transplant recipients with genotypes 1 or 4, the August 2020 AASLD/IDSA states that Harvoni (ledipasvir/sofosbuvir) may be given without ribavirin for post-liver transplant recipients with compensated cirrhosis or without cirrhosis.

1. **Compensated Liver Disease**:
   According to the American Association for the Study of Liver Diseases (AASLD 2017), the specific criteria for compensated liver disease include all of the following: a total bilirubin; serum albumin; prothrombin time/INR; presence of ascites; and presence of hepatic encephalopathy. However, these criteria do not establish a comprehensive definition of compensated liver disease. The AASLD guidance refers to compensated liver disease as Class A based on the Child Pugh-Turcotte (CPT) classification scoring system.

   Moderate to Severe (Decompensated) Liver Disease:
   The AASLD guidance refers to decompensated (moderate to severe) liver disease as Class B or C based on the Child-Pugh Turcotte (CPT) classification scoring system.

Child Pugh Classification (AASLD/IDSA 2016)

Parameters			
Points Assigned	1 point	2 points	3 points
Total Bilirubin (µmol/L)	<34	34-50	>50
Serum Albumin (g/L)	>35	28-35	<28
Prothrombin time/INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic Encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Child Pugh Score Interpretation (AASLD/IDSA 2009, 2016)

Class A	5-6 points	Well compensated liver disease
Class B	7-9 points	Significant functional compromise (moderate hepatic impairment)
Class C	10-15 points	Uncompensated liver disease (severe hepatic impairment)

2. Past Treatment Exposure Definitions (AASLD/IDSA 2017):
   a. NS5A Inhibitor: includes daclatasvir, ledipasvir, elbasvir, ombitasvir, pibrentasvir, or velpatasvir-containing regimens
   b. P/R: includes peginterferon (or non-pegylated interferon) ± ribavirin
   c. NS3/4A Protease Inhibitor: includes simeprevir, grazoprevir, paritaprevir, glecaprevir, and voxilaprevir-containing regimens
   d. Triple therapy: includes NS3 protease inhibitor (simeprevir, boceprevir or telaprevir) plus peginterferon and ribavirin
   e. Direct Acting Antiviral (DAA): includes NS5A inhibitors, NS3/4A protease inhibitors, and NS5B polymerase inhibitors (sofosbuvir, dasabuvir)
   f. P/R/S: includes peginterferon (or non-pegylated interferon) ± ribavirin ± sofosbuvir

3. Chronic Kidney Disease (CKD) Definitions (AASLD/IDSA 2017):
   Severe CKD (Stage 4): eGFR 15-29 mL/min
   End-Stage CKD (Stage 5): eGFR < 15 mL/min

4. **Metavir Scoring Systems for Fibrosis Staging (AASLD 2009):**

Stage (F)	Metavir
0	No fibrosis
1	Periportal fibrotic expansion
2	Periportal septae 1 (septum)
3	Porto-central septae
4	Cirrhosis

5. Hepatitis C virus (HCV) direct acting antiviral (DAA) agents have a black box warning for risk of hepatitis B virus (HBV) reactivation in individuals with HCV-HBV co-infection. Individuals should be tested for evidence of current or prior HBV infection prior to initiation of DAA therapy. HBV reactivation has been reported in HCV/HBV co-infected individuals currently taking or previously completed DAA therapy and not concomitantly receiving HBV antiviral therapy. Some cases of HBV reactivation have led to fulminant hepatitis, hepatic failure, and death. Individuals should be monitored for hepatitis flare or HBV reactivation during and following HCV DAA therapy. Individuals should be appropriately managed for HBV infection as indicated.

Key References:

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5. American Association for the Study of Liver Diseases and the Infectious Disease Society of America, in collaboration with the International Antiviral Society-USA. Recommendations for testing, managing and treating hepatitis C. Available at http://www.hcvguidelines.org/. Published on: January 29, 2014. Updated on: September 29, 2021. Accessed on: January 26, 2022.
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7. Kamal SM. Acute hepatitis C: a systematic review. Am J Gastroenterol. 2008;103(5):1283-1297.
8. U.S. Department of Health and Human Services AIDSinfo treatment guidelines. Considerations for Antiretroviral Use in Patients with Coinfections. Available at https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/26/hcv-hiv. Accessed on: January 13, 2021.
9. Wyles D, Weiland O, Yao B, et al. Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C virus infection. J Hepatol. 2019;70(5):1019-1023.