



BlueCross BlueShield
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Harvoni (sofosbuvir/ledipasvir)

Policy Number: 5.02.518
Origination: 10/2014

Last Review: 10/2014
Next Review: 10/2015

Policy

BCBSKC will provide coverage for Harvoni (sofosbuvir/ledipasvir) when it is determined to be medically necessary because the following criteria are met.

When Policy Topic is covered:

The use of Harvoni may be considered **medically necessary** for the following:

Food and Drug Administration (FDA)-Approved Indications

1. **Chronic Hepatitis C (CHC) Genotype 1 – Adults.** Approve for the specified duration below if patients meet all of the following criteria (a, b, c, and d):
 - a) The patient is \geq 18 years of age; AND
 - b) The patient does not have hepatocellular carcinoma (HCC) awaiting liver transplant (see Criteria 2); AND
 - c) The patient does not have recurrent hepatitis C virus (HCV) post-liver transplantation (see Criteria 3); AND
 - d) Harvoni is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
 - e) **According to the prescribing physician** the patient meets ONE of the following conditions (i, ii, or iii):
 - i. The patient has been documented as having a hepatic fibrosis score correlating with **Metavir Stage F3 or F4** as assessed by an invasive (liver biopsy) OR non-invasive method (e.g., aspartate aminotransferase-to-platelet ratio index [APRI] score, fibrosis-4 index [FIB-4], FibroScan, FibroTest/FibroSURE); OR
 - ii. The patient has **severe extrahepatic manifestations** placing them at high risk for severe complications of their HCV (patient must meet criteria 1 or 2):
 - (1) Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (e.g., vasculitis); OR
 - (2) Proteinuria, nephrotic syndrome, or membranoproliferative glomerular nephritis; OR
 - iii. The patient meets BOTH of the following conditions (1 and 2):
 - (1) The patient is at **high-risk of transmitting HCV** (patient must meet ONE of the following criteria a or b):
 - a. The patient is on long-term (\geq 3 months) hemodialysis; OR
 - b. The patient is a healthcare worker whose daily activities put them in contact with blood and/or needles; AND
 - (2) The patient has been counseled on ways to decrease transmission of HCV and minimize the risk of reinfection with HCV; AND
 - f) The patient meets ONE of the following criteria (i, ii or iii):
 - i. **Approve for 8 weeks** in patients who meet all of the following (1, 2 and 3):
 - (1) The patient is treatment-naïve; AND
 - (2) The patient does not have cirrhosis; AND
 - (3) Baseline HCV RNA is $<$ 6 million IU/mL. OR
 - ii. **Approve for 12 weeks** in patients who meet one the following (1, 2, 3 or 4);

- (1) The patient is treatment-naïve AND does not meet criterion f) i (this would include patients who are treatment-naïve with cirrhosis regardless of baseline HCV RNA or treatment-naïve patients without cirrhosis and baseline HCV RNA \geq 6 million IU/mL); OR
 - (2) The patient has previously been treated for HCV with peginterferon and ribavirin (PR) \pm HCV protease inhibitor (i.e., Incivek, Victrelis, or Olysio) and does not have cirrhosis (for patients with cirrhosis see *Criteria f) iii*); OR
 - (3) The patient is a prior relapser to Sovaldi/ribavirin (R) \pm pegylated interferon⁹⁻¹⁰ (with or without cirrhosis); OR
 - (4) The patient is a prior relapser to Sovaldi/Olysio \pm R (with or without cirrhosis).¹⁰ OR
- iii. **Approve for 24 weeks** in patients who meet the following criterion (1):
- (1) The patient has previously been treated for HCV with PR \pm HCV protease inhibitor (e.g., Incivek, Victrelis, or Olysio) and has cirrhosis.

Note: Retreatment with Harvoni is NOT recommended for the following groups of patients (See *Conditions Not Recommended for Approval*): Null or partial responders to Sovaldi/R \pm pegylated interferon, patients previously treated with Sovaldi/Olysio \pm R, and patients who have previously received treatment with Harvoni).

Harvoni is indicated for the treatment of genotype 1 CHC in adults.¹ The recommended duration of treatment is 12 weeks in treatment-naïve patients with or without cirrhosis; 8 weeks of treatment may be considered in treatment-naïve patients without cirrhosis who have a baseline HCV RNA $<$ 6 million IU/mL. In treatment-naïve patients without cirrhosis who had a baseline viral load (HCV RNA) $<$ 6 million IU/mL, in the ION-3 study, relapse rates between patients who received 8 weeks of Harvoni vs. 12 weeks of Harvoni were identical (2% in each group, respectively).¹ In treatment-naïve patients without cirrhosis who had a baseline HCV RNA \geq 6 million IU/mL, the rate of relapse was greater in those treated with 8 weeks of Harvoni compared to 12 weeks of Harvoni (10% vs. 1%, respectively). ION-3 did not include patients with cirrhosis (Metavir F4) or previously treated patients, and therefore, recommendations for 8 weeks in patients with cirrhosis or for those previously treated cannot be provided. In treatment-experienced patients (prior treatment with PR or prior treatment with PR + HCV protease inhibitor) the recommended duration of therapy is 12 weeks for patients without cirrhosis and 24 weeks for patients with cirrhosis.

Data to support the approval of Harvoni in prior relapsers to Sovaldi/R \pm pegylated interferon or Sovaldi/Olysio \pm R come from two small unpublished studies.⁹⁻¹⁰ In a small study (n = 14), available as an abstract only (SYNERGY), Harvoni was studied in relapsers to Sovaldi/R (treated for 24 weeks). Patients were retreated with Harvoni for 12 weeks. SVR 12 was achieved in all 14 patients.⁹ In a Phase II open-label study (ELECTRON-2) of Harvoni \pm R for 12 weeks in HCV genotype 1 prior relapsers (prior relapsers to Sovaldi/R \pm DAA) [n = 19]; SVR 12 was achieved in all 19 patients.¹⁰ Presently there are no data to support the use of Harvoni in other Sovaldi retreatment populations.

In the opinion of expert physicians reviewing the data, we have adopted criteria for whom to treat and for retreatment in some patients who have received prior therapy with Sovaldi.

Other Uses with Supportive Evidence

2. **CHC – Adults with HCC Awaiting Liver Transplantation, Genotype 1.** Approve for the specified duration in patients who meet the following criteria (a, b, c, d and e):
- a) The patient is \geq 18 years of age; AND
 - b) The patient has HCC; AND
 - c) The patient is awaiting liver transplantation (patient is on the list for liver transplant); AND
 - d) Harvoni is prescribed by or in consultation with one of the following prescribers who is affiliated with a liver transplant center²: a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
 - e) The patient meets ONE of the following criteria (i or ii):

- i. **Approve for 12 weeks** in patients who meet one of the following criteria (1 or 2):
 - (1) The patient is treatment-naïve; OR
 - (2) The patient has previously been treated for HCV AND does not have cirrhosis; OR
- ii. **Approve for 24 weeks** in patients who have previously been treated and have cirrhosis.

In the opinion of an expert physician we have adopted criteria for adults with HCC awaiting liver transplantation.

- 3. **Recurrent HCV Post-Liver Transplantation – Adults, Genotypes 1.** Approve for the specified duration in patients who meet the following criteria (a, b, c and d):
 - a) The patient is ≥ 18 years of age; AND
 - b) The patient has recurrent HCV after a liver transplantation; AND
 - c) Harvoni is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center²: a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND;
 - d) The patient meets ONE of the following criteria (i or ii):
 - i. **Approve for 12 weeks** in patients who meet one of the following criteria (1 or 2):
 - (1) The patient is treatment-naïve *for recurrent HCV*; OR
 - (2) The patient has previously been treated *for recurrent HCV* AND does not have cirrhosis; OR
 - ii. **Approve for 24 weeks** in patients who have previously been treated *for recurrent HCV* and have cirrhosis.

In the opinion of an expert physician reviewing the data, we have adopted the criteria for recurrent HCV post-liver transplantation.

- 4. **Patient Has Been Started on Harvoni.** Approve 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 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).

When Policy Topic is not covered:

The use of Harvoni is considered **investigational** for all other indications including:

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. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **CHC (any genotype), Combination with Any Other DAAs (e.g., Incivek, Victrelis, Olysi, Sovaldi) [Not Including Ribavirin].** Harvoni provides a complete antiviral regimen for patients with genotype 1 HCV. Harvoni is not recommended to be used with other products containing sofosbuvir. Although not indicated, Harvoni has been studied with ribavirin; however, co-administration of Harvoni/R did not provide greater rates of SVR. In the opinion of a specialist physician reviewing the data we have adopted this criterion.
2. **CHC, Non-Genotype 1.** Harvoni is not indicated for non-genotype 1 CHC. There are ongoing trials in various patient populations, including patients with genotype 3.¹⁰ The optimal combination (with or without ribavirin) and duration of therapy has not been established. Additional data are needed. In the opinion of a specialist physician reviewing the data we have adopted this criterion.
3. **Life Expectancy < 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, little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (less than 12 months) due to non-liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence.

4. **Pediatric Patients (Age < 18 Years).** The safety and efficacy of Harvoni have not been established in pediatric patients < 18 years of age.¹ In the opinion of a specialist physician reviewing the data we have adopted this criterion.
5. **Retreatment of Null or Partial responders to Sovaldi/R ± Pegylated Interferon or Sovaldi/Olysio ± R.** There are no data demonstrating efficacy of Harvoni in patients with a prior null or partial response to Sovaldi/R ± pegylated interferon or Sovaldi/Olysio ± R. Limited data exist for prior relapsers and such patients are reviewed above in the approval criteria.⁹⁻¹⁰ In the opinion of a specialist physician reviewing the data we have adopted this criterion.
6. **Retreatment in Patients Who Have Previously Received Harvoni** (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). According to the AASLD/IDSA/IAS-USA guidance, a small number of patients in whom an initial antiviral treatment has failed have achieved SVR when treated with the same drugs for a longer duration (the referenced study addressed HCV protease inhibitor + PR failures), or when treated with alternative antiviral regimens.² Thus, patients in whom treatment has failed to achieve an SVR should be considered for treatment when alternative antiviral regimens are available. In the opinion of a specialist physician reviewing the data we have adopted this criterion.
6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Considerations

Harvoni requires prior authorization through the Clinical Pharmacy Department.

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Hayes Medical Technology Directory, Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

Description of Procedure or Service

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 the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.¹ Ledipasvir has potency against genotype 1a and 1b; sofosbuvir has potency against genotypes 1 through 6.

Dosing

The recommended dosage of Harvoni is one tablet taken orally once daily (QD) with or without food.¹ Because relapse rates are determined by baseline and host viral factors, treatment durations differ between certain subgroups. Table 1 below provides the recommended Harvoni treatment durations for treatment-naïve and treatment-experienced patients and those with and without cirrhosis.

Table 1. Recommended Treatment Duration for Harvoni in Patients with CHC Genotype 1.¹

Patient Population	Duration of treatment
Treatment-naïve with or without cirrhosis	12 weeks*
Treatment-experienced** without cirrhosis	12 weeks
Treatment-experienced** with cirrhosis	24 weeks

CHC – Chronic hepatitis C virus; * Harvoni for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment 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.

Rationale

Guidance

Sovaldi, one of the components of Harvoni is prominently featured in the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA)/International Antiviral Society-USA (IAS-USA) web-based recommendations for testing, managing, and treating hepatitis C (last updated October 8, 2014).² Harvoni is not yet incorporated into recommendations and the guidance should be consulted for the [most up-to-date information](#).

Who to Treat

On August 11, 2014, the AASLD guidance was updated to provide recommendations on whom to treat.²

Because of the many benefits associated with successful treatment, clinicians should treat hepatitis C virus (HCV)-infected patients with antiviral therapy with the goal of achieving sustained viral response (SVR), preferably early in the course of their chronic HCV infection before the development of severe liver disease and other complications.

Fibrosis

An accurate assessment of fibrosis is vital in assessing the urgency for treatment. The degree of hepatic fibrosis is one of the most robust prognostic factors used to predict disease progression and clinical outcomes. Those with substantial fibrosis (defined as Metavir F2 or higher) should be given priority for therapy in an effort to decrease the risk of clinical consequences such as cirrhosis, liver failure, and HCC. However, those with severe fibrosis (Metavir stage F3 or F4) are most in need of immediate therapy. Although liver biopsy is the diagnostic standard, sampling error and observer variability limit test performance. In addition, the test is invasive and minor complications are common, limiting patients and practitioner acceptance. Although rare, serious complications such as bleeding are well-recognized. Non-invasive tests to stage the degree of fibrosis in patients with CHC include models incorporating indirect serum biomarkers, direct serum biomarkers, and vibration-controlled transient liver elastography. No single method is recognized to have high accuracy alone and each test must be interpreted carefully. The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography. Alternatively, if direct biomarkers or vibration-controlled transient liver elastography are not available, the aspartate aminotransferase-to-platelet ratio index (APRI) or fibrosis-4 index (FIB-4) can help identify those most likely to have F3 or F4 fibrosis stage.

Treatment is assigned highest priority for patients with advanced fibrosis (Metavir F3), patients with compensated cirrhosis (Metavir F4) [Class I, Level A for Metavir F3 and F4], liver transplant recipients (Class I, Level B), and patients with severe extrahepatic manifestations of HCV (Class I, Level B for Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations [e.g., vasculitis] and Class IIa, Level B for proteinuria, nephrotic syndrome, or membranoproliferative glomerularnephritis). The most immediate and high-impact benefits of SVR will be realized by populations that are at highest risk for liver-related complications due to progressive liver disease (Metavir F3 or F4) and transplant

recipients or those with clinically severe extrahepatic manifestations. Other populations at high risk for liver disease progression (Metavir F2) or with substantial extrahepatic manifestations are also expected to derive appreciable benefits, although the time course for realizing such benefits may be delayed. SVR will also remove the risk of further transmission of HCV. Treatment of individuals at high-risk to transmit HCV to others may yield long-term future benefits from decreased transmission and a potential decrease in HCV prevalence.

For persons with advanced liver disease (Metavir F3 or F4), the risk of developing complications of liver disease such as hepatic decompensation or hepatocellular carcinoma (HCC) is substantial and may occur in a relatively short time frame. Many studies have demonstrated that hepatitis C therapy and the achievement of an SVR in this population results in dramatic decreases in hepatic decompensation events, HCC, and liver-related mortality. Importantly, individuals with advanced liver disease continue to require long-term follow-up and HCC surveillance regardless of treatment outcome.

Fibrosis progression is variable across different patient populations as well as within the same individual over time. Many of the components that determine fibrosis progression and development of cirrhosis in an individual are unknown. However, co-infection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) and prevalent co-existent liver disease (e.g., non-alcoholic steatohepatitis [NASH]), are well-recognized contributors to accelerated fibrosis progression. Patients with these conditions should be prioritized for HCV therapy (Class I, Level B for HIV, Class I, Level B for HBV, and Class IIa, Level C for NASH).

Extrahepatic Manifestations

CHC is associated with a syndrome of cryoglobulinemia and an immune complex and lymphoproliferative glomerular nephritis, neurologic disease (e.g., peripheral neuropathy, central nervous system [CNS] vasculitis), and reduced complement levels.² Antiviral treatment should be prioritized for those with the syndrome of cryoglobulinemia and symptoms or objective evidence of end-organ manifestations. Successful treatment of HCV using interferon-based therapies can reverse proteinuria and nephrotic syndrome, but it does not fully improve azotemia. The high rates of the SVR with the direct-acting antivirals (DAAs) support their use in the management of HCV renal related disease.

High-Risk for Transmission

The prevalence of HCV infection is elevated in individuals on hemodialysis ranging from 7.8% to 8.9% in the US.² The seroprevalence has been found to increase with time on dialysis suggesting that nosocomial transmission, among other risk factors, plays a role in HCV acquisition in these patients. Further HCV infection in such patients has a detrimental impact on kidney transplantation outcomes (Class IIa, Level C for treatment).

Individuals who have successfully achieved an SVR no longer transmit the virus to others. Therefore, successful treatment benefits public health. Several health models have shown that even modest increases in successful treatment of HCV infection among persons who inject drugs can decrease prevalence and incidence. Successful treatment of HCV-infected individuals at greatest risk for transmission represents an important tool to help stop HCV transmission in those who continue to engage in high-risk behaviors. Injection drug use (IDU) accounts for the majority of new infections (approximately 70%) and is the key driving force in perpetuating the epidemic of HCV (Class IIa, Level C for treatment). Studies of interferon-containing treatment in injection drug users have shown comparable adherence and efficacy rates of patients who do not use injection drugs. Importantly the rate of reinfection in this population is lower than incident infection in the IDU population in general; however, reinfection increases with active or ongoing IDU and available data are limited in follow-up duration. Ideally, treatment of patients with HCV who inject drugs should be delivered in a multidisciplinary care setting with services to reduce the risk of reinfection and for management of the common social and psychiatric comorbidities in this population. Regardless of the treatment setting, recent and active IDU should not be seen as an absolute contraindication to HCV therapy. Treatment

of patients with HCV who inject drugs is necessary to positively impact the HCV epidemic in the US and globally.

In the past 10 years, there has been an increase in incident HCV infection among HIV-infected men who have sex with men (MSM) who did not report IDU as a risk factor.² Recognition and treatment of HCV in this population may represent an important step in preventing subsequent infections. As with persons who inject drugs, HIV-infected MSM with ongoing high-risk sexual practices should be treated for their HCV infection in conjunction with continued education on risk reduction strategies (Class IIa, Level C).

The seroprevalence of HCV ranges from 30% to 60% among incarcerated individuals. Treatment of such patients would likely decrease the prevalence of HCV infection in this at-risk population (Class IIa, Level C).

Patients Not Recommended for Treatment

In patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis, HCV therapy is not needed. Little evidence exists to support initiation of HCV treatment in patients with limited life expectancy < 12 months due to non-liver related comorbid conditions because such patients are unlikely to realize the benefits of HCV treatment.

What Treatment to Use

Harvoni has not yet been incorporated into the AASLD/IDSA/IAS-USA guidance. The Tables 2 and 3 below provide a brief overview of the placement of Sovaldi in the guidance for treatment-naïve and retreatment patients without other comorbidities. The guidance also addresses several unique patient populations. Patients with *compensated cirrhosis*, including those with *hepatocellular carcinoma* (HCC), should receive treatment as recommended for patients without cirrhosis (Class I, Level A).

Patients with *decompensated cirrhosis* (moderate or severe hepatic impairment; Child-Turcotte-Pugh [CTP] Class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center [Class I, Level C]). If the decision has been made to treat such patients, the recommended regimen for patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; CTP Class B or C) who may or may not be candidates for liver transplantation, including those with HCC should be used only by highly experienced HCV providers is: Sovaldi + R (with consideration of the patients CrCl and hemoglobin level) for up to 48 weeks (Class IIb, Level B). Any interferon-based therapy (Class III, Level A), monotherapy with peginterferon, ribavirin, or a DAA (Class III, Level A), or Incivek, Victrelis, or Olysio-based regimens (Class III, Level A) are not recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C). Table 4 provides recommendations for unique patient populations.

Table 2. Treatment of Genotype 1 HCV in Treatment-Naïve and Relapse Patients.²

Genotype	Recommended		Alternative		Not Recommended
	Interferon Eligible	Interferon Ineligible	Interferon Eligible	Interferon Ineligible	
1	Sovaldi + PR x 12 weeks (Class I, Level A)	Sovaldi + Olysio ± R x 12 weeks (Class I, Level B)	Olysio + PR x 24 weeks[†] (Class IIa, Level A)	Sovaldi + R x 24 weeks[‡] (Class IIb, Level B)	-PR ± Incivek or Victrelis x 24 to 48 weeks (Class IIb, Level A) -Monotherapy with P, R, or DAA.

Recommendations are regardless of genotype subtype unless otherwise indicated; HCV – Hepatitis C virus; PR – Peginterferon and ribavirin; R – Ribavirin; [†] Only recommended for patients with genotype 1a *without* the Q80K polymorphism or genotype 1b; [‡] Preliminary data suggest that this regimen may be less effective than Sovaldi + Olysio, especially in patients with cirrhosis; P – Peginterferon; DAA – Direct acting antiviral; NA – Not applicable;

Table 3. Treatment of HCV in Patients who are Prior Non-Responders (Null-Responders or Partial Responders).²

Genotype	Prior Treatment History	Recommended		Alternative		Not Recommended
		Interferon Eligible	Interferon Ineligible	Interferon Eligible	Interferon Ineligible	
1	PR only	Sovaldi + Olysio ± R x 12 weeks (Class IIa, Level B)		Olysio x 12 weeks + PR x 48 weeks[€] (Class IIa Level A)	N/A	-PR + Incivek or Victrelis (Class IIb, Level A) - Monotherapy with P, R, or DAA (Class III, Level A) -For non-responder patients with genotype 1 and a history of decompensated cirrhosis (moderate or severe hepatic impairment CTP class B or C), treatment is not indicated because of the risks of P, Victrelis, and Incivek in this population.
	HCV Protease Inhibitor + PR	N/A		Sovaldi x 12 weeks + PR x 12 to 24 weeks (Class IIb, Level C)	N/A	

Recommendations are regardless of genotype subtype unless otherwise indicated; HCV – Hepatitis C virus; PR – Peginterferon and ribavirin; R – Ribavirin; PR – Peginterferon and ribavirin; P – Peginterferon; R – Ribavirin; [€] All patients with cirrhosis who are receiving Olysio should have well compensated liver disease; DAA – Direct acting antiviral; CTP – Child Turocette Pugh; N/A – Not applicable.

Table 4. Treatment of Genotype 1 HCV in Unique Patient Populations.²

Genotype	Prior Treatment History	Recommended		Alternative		Not Recommended
		Interferon Eligible	Interferon Ineligible	Interferon Eligible	Interferon Ineligible	
<i>HIV Co-Infection</i>						
1	Naïve/Relapse	Sovaldi + PR x 12 weeks (Class I, Level B)	-Sovaldi R x 24 weeks (Class I, Level B) -Sovaldi + Olysio ± R x 12 weeks^β (Class IIa, Level C)	Olysio x 12 Weeks + PR x 24 Weeks^{†β} (Class IIa, Level B)	None.	-PR ± Incivek or Victrelis x 24 to 48 weeks (Class IIb, Level A) - Monotherapy with P, R, or DAA (Class III, Level A)
	Partial/Null-Response PR	Sovaldi + Olysio ± R x 12 weeks^β		Sovaldi + R x 12 weeks (Class IIb, Level C)	Sovaldi + R x 24 Weeks (Class IIb, Level C)	
	Partial/ Null Response Incivek or Victrelis + PR	Treat as recommended for HCV monoinfected patients.		N/A	N/A	
<i>Recurrent Hepatitis C After Liver Transplantation (Compensated or Decompensated Allograft HCV)</i>						
1	Treatment-naïve (naïve to treatment post transplant)	Sovaldi + Olysio ± R x 12 to 24 weeks (Class IIb, Level C)		Sovaldi + R ± P x 24 weeks (Class IIb, Level C)		-Monotherapy with P, R, or DAA (Class III, Level A) -Incivek or Victrelis-based regimens (Class III, Level A)

HCV – Hepatitis C virus; HIV – Human immunodeficiency virus; PR – Peginterferon and ribavirin; ^β Olysio should only be used with antiretroviral drugs with which it does not have significant interactions; [†] Only recommended for patients with genotype 1a without the Q80K polymorphism or genotype 1b; P – Peginterferon; R – Ribavirin; DAA – Direct acting antiviral; N/A – Not applicable; ^a Recommendations are regardless of genotype subtype unless otherwise indicated; PR – Peginterferon and ribavirin; P – Peginterferon; R – Ribavirin; DAA – Direct acting antiviral; NA – Not applicable; ^a Few data are available to help guide decision making in patients infected with genotype 4, 5 or 6 CHC.

Rationale for Approval Criteria

Summary of Pivotal Trial Data in Patients with Genotype 1 CHC

The efficacy of Harvoni was established in three Phase III, randomized, open-label, multicenter, pivotal studies in patients with genotype 1 CHC (ION 1, 2, and 3).³⁻⁸ The primary endpoint for all three studies was the proportion of patients who achieved sustained viral response 12 weeks after completion of therapy (SVR12). Various subgroups were also assessed for SVR12. Across all subgroups examined as well as in the overall population, Harvoni provided superior rates of SVR12 over historical control in previously untreated patients as well as patients who had received prior therapy with peginterferon/ribavirin (PR) ± HCV protease inhibitor (PI). Rates of SVR12 were also high in patients with cirrhosis (ION 1 and 2 only [ION 3 did not include patients with cirrhosis]).

ION-1 (n = 870; treated n = 865) assessed the efficacy of four Harvoni regimens in HCV **treatment-naïve** adults (Harvoni QD ± weight-based ribavirin [WBR] twice daily [BID] for 12 weeks and Harvoni QD ± WBR BID for 24 weeks).³⁻⁴ The rates of SVR12 in all four treatment groups were superior to the historical control rate of 60% (P < 0.001 for all comparisons). The rates of SVR12 for each of the four treatment groups were as follows: 99% for Harvoni for 12 weeks, 97% for Harvoni + WBR for 12 weeks, 98% for Harvoni for 24 weeks, and 99% for Harvoni + WBR for 24 weeks.

ION-2 (n = 441; treated n = 440) assessed the efficacy of the same four Harvoni regimens as ION-1; however, ION-2 studied the regimens in patients who had **previously been treated with PR ± HCV PI**.⁵⁻⁶ In all four treatment groups, the rate of SVR12 was superior to the adjusted historical response rate of 25% (P < 0.001 for all comparisons). The rates of SVR12 for each of the four treatment groups were as follows: 94% for Harvoni for 12 weeks, 96% for Harvoni + WBR for 12 weeks, 99% for Harvoni for 24 weeks, and 99% for Harvoni + WBR for 24 weeks. The difference between the rates of response among patients with cirrhosis who received 12 weeks of treatment and the rates among patients with cirrhosis who received 24 weeks of treatment was significant (P = 0.007). The rate of SVR12 in patients with cirrhosis was as follows: 86.4% (95% CI: 65%, 97%) for Harvoni 12 weeks (n = 19/22), 81.8% (59.7%, 94.8%) for Harvoni + WBR 12 weeks (n = 18/22), 100% (95% CI: 84.6%, 100%) for both Harvoni 24 week treatment groups (with or without ribavirin) [n = 22/22 for both groups].⁵ The absence of cirrhosis was identified as the only baseline factor associated with a significant increase in the rate of response.⁶

ION-3 (n = 647), assessed the efficacy of three Harvoni regimens in HCV **treatment-naïve** adults **without cirrhosis** (Harvoni QD for 8 weeks, Harvoni QD + WBR BID for 8 weeks, or Harvoni QD for 12 weeks).⁷⁻⁸ In all three treatment groups, the rates of SVR12 were superior to the adjusted control rate of 60% (P < 0.001 for all comparisons). The rates of SVR12 for Harvoni QD for 8 weeks, Harvoni QD + WBR BID for 8 weeks, or Harvoni QD for 12 weeks were 94%, 93%, and 95%, respectively. In the secondary analysis the rate of SVR12 among patients who received 8 weeks of Harvoni without WBR was non-inferior to the response rates in the other two treatment groups.

Relapsers to Sovaldi/R

In a small study (n = 14), available as an abstract only SYNERGY in which Harvoni was studied in relapsers to Sovaldi/R (treated for 24 weeks). Patients were retreated with Harvoni for 12 weeks. SVR 12 was achieved in all 14 patients.⁹

In a Phase II open-label study (ELECTRON-2) of Harvoni ± R for 12 weeks in HCV genotype 1 prior relapsers (prior relapsers to Sovaldi/R ± DAA) [n = 19]; SVR 12 was achieved in all 19 patients.¹⁰

According to the AASLD/IDSA/IAS-USA guidance, a small number of patients in whom an initial antiviral treatment failed have achieved SVR when treated with the same drugs for a longer duration (the referenced study addressed PI+PR failures), or when treated with alternative antiviral regimens.² Thus, patients in whom treatment has failed to achieve an SVR should be considered for treatment when alternative antiviral regimens are available.

Patients in whom antiviral therapy failed to achieve an SVR may harbor viruses that are resistant to one or more of the antivirals at the time of virologic “breakthrough.” However, there is no evidence to date that the presence of resistance-associated variants (RAVs) results in more progressive liver injury than would have occurred if the patient did not have resistant viruses. Furthermore, RAVs are often not detectable with routine (population sequencing) detection methods, nor with more sensitive tests of HCV variants, after patients are followed up for several months. Subsequent retreatment with combination antivirals, particularly regimens containing antiviral drugs that have a high barrier to resistance, such as nucleotide polymerase inhibitors (e.g., sofosbuvir), may overcome the presence of resistance to one or more antivirals. With the exception of testing for Q80K polymorphism at baseline in patients with HCV genotype 1a before treatment with Olysio/PR, testing for RAVs prior to repeat antiviral treatment is not recommended. If in doubt, consultation with an expert in the treatment of HCV infection may be useful.

HCC Awaiting Liver Transplant

The efficacy of Harvoni in the pre- and post-transplant setting is being evaluated in patients with chronic genotype 1 or 4 HCV infection.¹¹ Participants will be randomized to receive 12 or 24 weeks of dosing with Harvoni + WBR. The primary endpoint is the proportion of patients with SVR12. Several cohorts are enrolled to encompass patients with advanced liver disease without transplant and those in the post liver transplant setting.

The efficacy of Sovaldi has been established in patients with HCV genotype 1 (2, 3, or 4) infection, including those with HCC meeting Milan criteria (awaiting liver transplantation).^{1,12-14} Sovaldi should be used in combination with ribavirin for treatment of CHC in patients with HCC awaiting liver transplantation for up to 48 weeks or until liver transplantation, whichever occurs first. Sovaldi has not been studied in other populations awaiting liver transplantation.

The AASLD guidelines do address the availability of Harvoni in the pre-transplant setting. The guidelines note that if the decision to treat has been made, the recommended regimen is Sovaldi R for 48 week (Class IIb, Level B). Patients should be referred to a medical practitioner with expertise in treating this condition (ideally in a liver transplant center) [Class I, Level C].

Recurrent HCV Post Liver Transplantation

The AASLD guidelines do not address the availability of Harvoni in the post-transplant setting. The guidelines recommend Sovaldi with Olysio ± for 12 to 24 weeks in patients with genotype 1 in the allograft liver, including those with compensated cirrhosis (Class IIb, Level C).² The alternative regimen for treatment-naïve patients with genotype 1 HCV in the allograft liver is Sovaldi with ribavirin with or without peginterferon for 24 weeks (Class IIb, Level C).

Other

There are no data assessing the efficacy of Harvoni specifically in the case of occupational exposure to HCV. Occupational exposure via skin injury potentially causes up to 16,000 new cases of HCV annually with nurses experiencing the highest exposure rates, followed by medical residents.¹⁵ Fatigue and deviations from infection control practices are contributing factors. Most of these injuries can be prevented by standard precautions, the use of protective gowns and goggles, increased awareness and strict supervision. The average rate of seroconversion after an occupational exposure to HCV-infected blood through accidental needle stick is 1.8%.

References:

1. Harvoni® tablets [prescribing information]. Foster City, CA: Gilead; December 2013.
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 October 8, 2014. Accessed on: October 8, 2014.
3. Afdahl N, Zeuzem S, Chojkier M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med.* 2014 April 12 [Epub ahead of print].

4. Supplement to: Afdhal N, Zeuzem S, Kwo P, et al. Sofosbuvir and Ledipasvir for 12 or 24 Weeks in Previously Untreated HCV Genotype 1. *N Engl J Med.* 2014 April 12 [Epub ahead of print].
5. Afdhal N, Reddy KR, Nelson DR, et al; for the ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med.* 2014 April 12 [Epub ahead of print].
6. Supplement to: Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med.* 2014 April 12 [Epub ahead of print].
7. Kowdley KV, Gordon SC, Reddy KR, et al; for the ION-3 Investigators. Ledipasvir and sofosbuvir for 8 to 12 weeks for chronic HCV without cirrhosis. *N Engl J Med.* 2014 April 11 [Epub ahead of print].
8. Supplement to: Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med.* 2014 April 11 [Epub ahead of print].
9. Data on file. Gilead Sciences. SYNERGY trial. August 2014.
10. Data on file. Gilead Sciences. ELECTRON-2 trial. August 2014.
11. GileadLeditasvir/sofosbuvir fixed-dose combination + ribavirin in subjects with chronic HCV with advanced liver disease or post-liver transplant. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2014 Oct 6]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01938430?term=ledipasvir%2Fsofosbuvir&rank=7> NLM Identifier: NCT01938430.
12. Curry MP, Forns X, Chung RT, et al. Pretransplant sofosbuvir and ribavirin to prevent recurrence f HCV infection after liver transplantation [abstract #213]. Presented at: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; Washington, DC; November 1-5, 2013.
13. Curry MP, Forns X, Chung RT, et al. Pretransplant sofosbuvir and ribavirin to prevent recurrence f HCV infection after liver transplantation [oral presentation #213]. Presented at: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; Washington, DC; November 1-5, 2013.
14. Data on file. Sofosbuvir development program. Gilead Sciences. November 20, 2013.
15. Negro F. *inPractice*[®] - Hepatitis C virus transmission to healthcare workers. Last reviewed: 07/30/2014. Available at: http://www.inpractice.com/Textbooks/Hepatology/ch7_Hepatitis_C_Epidemiology_Pathogenesis_Diagnosis_and_Natural_History/Chapter-Pages/Page-2/subpage-6.aspx. Accessed on: 09/08/2014.

Billing Coding/Physician Documentation Information

NA Harvoni is a pharmacy benefit

Additional Policy Key Words

Policy Number: 5.02.518

Related Topics

N/A

Policy Implementation/Update Information

10/2014 New Policy titled Harvoni (sofusbuvir/ledipasvir)

This Medical Policy is designed for informational purposes only and is not an authorization, an explanation of benefits, or a contract. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there is any exclusion or other benefit limitations applicable to this service or supply. Medical technology is constantly changing and Blue Cross and Blue Shield of Kansas City reserves the right to review and revise medical policy. This information is proprietary and confidential and cannot be shared without the written permission of Blue Cross and Blue Shield of Kansas City.