Ledipasvir/Sofosbuvir (Harvoni) for Treatment of Hepatitis C

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Line(s) of Business: HMO; PPO; QUEST Integration
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Section: Prescription Drugs
Place(s) of Service: Office; Outpatient

I. Description

The diagnosis of chronic hepatitis C virus (HCV) infection is based on the presence of both anti-HCV antibodies, detected by enzyme immunoassays, and HCV RNA, detected by molecular amplification (polymerase chain reaction). HCV RNA can be detected in blood within 1 to 3 weeks after exposure, and anti-HCV seroconversion occurs by 8 to 9 weeks.

Progression of chronic hepatitis C infection to end stage liver disease most commonly occurs over several decades. Early in the course of infection, serum levels or liver-related enzymes, such as alanine aminotransferase, aspartate aminotransferase, and \( \gamma \)-glutamyltransferase, may be elevated but there are no signs of liver dysfunction. As the disease progresses, signs of liver fibrosis may develop, and fibrosis will often progress to cirrhosis. Many patients, on the other hand, may go decades or a lifetime without substantial damage. Early damage to the liver, including fibrosis, is generally reversible, while cirrhosis may not be reversible. Disease progression is accelerated in the presence of cofactors such as alcohol consumption, diabetes mellitus, older age at acquisition, HIV coinfection, and coinfection with other hepatic viruses.

An assessment of the severity of hepatic fibrosis is important for treatment and prognosis of chronic HCV infection, the METAVIR fibrosis scoring system (0-4) is used to stage and grade hepatic fibrosis (refer to Appendix A).

Direct acting antiviral (DAA) medications for hepatitis C specifically target proteins involved in the HCV life cycle and disrupt viral replication. In patients with chronic hepatitis C, these medications offer the potential to improve cure rates with lower toxicity compared with treatment regimens that do not include DAAs.
DAA medications for the treatment of hepatitis C
Simeprevir (Olysio) is indicated as a combination treatment with PegIFNα and RBV in HCV genotype 1 infected patients with compensated liver disease (including cirrhosis).

Sofosbuvir (Sovaldi) is indicated for the treatment of HCV infection as a component of a combination antiviral treatment regimen. The efficacy of sofosbuvir has been established in patients with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) (refer to Appendix B) and those with HCV/HIV-1 co-infection.

Ledipasvir/Sofosbuvir (Harvoni) is the first all-oral, interferon-free regimen and is indicated for the treatment of HCV genotype 1 infected patients.

II. Criteria/Guidelines
A. Ledipasvir/Sofosbuvir (Harvoni) is covered for the treatment of HCV infection (subject to Limitations and Administrative Guidelines) when all of the following criteria are met:
   1. The patient is at least 18 years of age
   2. The patient has an HCV genotype 1 infection
   3. The prescribing physician attests that the patient is at low risk for noncompliance with the treatment regimen
   4. The patient has an HCV RNA positive diagnosis documented by a quantitative titer obtained within the previous 3 months
   5. The patient has no history of alcohol or substance abuse within the 6 months prior to treatment
   6. The patient has ONE of the following:
      a. Liver biopsy with a METAVIR score of F3 or F4
      b. Transient elastography (Fibroscan) score greater than or equal to 9.5 kPa
      c. FibroTest (e.g., FibroSure) score of greater than or equal to 0.58
      d. Radiological imaging consistent with cirrhosis (e.g., evidence of portal hypertension)
      e. Ascites
      f. Esophageal varices
      g. Serious extrahepatic manifestations of hepatitis C, such as cryoglobulinemia
   7. The medication is being prescribed by, or in consultation with, ONE of the following specialists:
      a. Hepatologist
      b. Gastroenterologist
      c. Infectious Disease Specialist
8. The patient agrees to the following:
   a. 100% medication compliance
   b. Regular follow-up with specialty pharmacist or treating provider
   c. No alcohol or illicit drug using during the course of treatment
   d. Drug testing, when recommended by the treating provider
   e. Blood draws to measure HCV RNA, when ordered

9. Treatment regimen is in accordance with FDA approved treatment regimens (refer to Appendix C).

B. Ledipasvir/Sofosbuvir (Harvoni) is covered for the treatment of HCV infection (subject to Limitations and Administrative Guidelines) regardless of the degree of liver fibrosis when the above criteria (A.1-5, 7-9) are met for health care workers who are HCV positive and, because they perform invasive procedures, are at significant risk of transmitting the infection to patients.

III. Limitations

A. Treatment of HCV with ledipasvir/sofosbuvir (Harvoni) is not covered when any of the criteria specified above (II.A-B) are not met. Treatment may be contraindicated in individuals when any of the following indications are present:

1. Uncontrolled depression (for example, suicide risk); or
2. Pregnant women or those who may plan to become pregnant during the course of treatment; or
3. Known hypersensitivity to drugs used to treat hepatitis C; or
4. Decompensated liver disease as defined by Child-Pugh score greater than 6 (refer to Appendix D) except for patients who are active candidates for liver transplantation; or
5. Hepatocellular carcinoma except for patients who are active candidates for liver transplantation, including meeting Milan criteria; or
6. Glomerular filtration rate (GFR) is less than 30.

B. Treatment will be discontinued if HCV RNA results are greater than 25 IU/ml at 4 weeks after the initiation of treatment and the provider attests to patient noncompliance

C. Coverage will generally be limited to one treatment per lifetime. Repeat treatments for any of the following will generally not be covered:
1. Inadequate compliance resulting in failure to achieve sustained viral response (SVR)
2. Reinfection
3. Discontinuation of treatment secondary to harmful alcohol and/or drug abuse
4. A prior treatment failure when there is no recognized, effective retreatment regimen

D. The plan will not cover replacement medication for pills that are lost or stolen.

IV. Administrative Guidelines

A. For 12 and 24 week treatment durations, the following precertification requirements apply:
   1. Precertification is required for the initial 6 weeks of treatment. To precertify, contact CVS Specialty Guideline Management at (808) 254-4414.
   2. Precertification is required for continuation of treatment up to an additional 6 weeks.
   3. The HCV RNA results at 4 weeks after the commencement of treatment must be submitted with the continuation request.

B. For 8 week treatment durations, precertification is required for the 8 weeks of treatment. To precertify, contact CVS Specialty Guideline Management at (808) 254-4414.

C. The following medical record documentation, as applicable to the patient, must be submitted with the initial precertification request:
   1. Written treatment plan from the requesting provider
   2. Documentation that the member has been assessed for potential non-adherence to treatment regimen

D. A specialty pharmacy will dispense no more than 28 days of medication at one time although 14 days is preferred.

E. The HMSA Hepatitis C Treatment Checklist can be found in Appendix E. This checklist, completed and signed by the patient, is required prior to treatment.

F. This policy is not applicable to Akamai Advantage members.

G. This policy is not applicable to QUEST Integration ABD members.

V. Scientific Background

First-generation Direct Acting Antivirals (DAA)

The first-generation DAAs, boceprevir and telaprevir, have demonstrated superior SVR compared with standard therapy with IFN/RBV. Treatment response, defined as a SVR at 12 or 24 weeks, was achieved in the 60% to 80% range across various trials of boceprevir and telaprevir. Adverse events (AEs) occur at a relatively high rate with these agents. Serious adverse events (SAEs) can involve skin reactions, and hematologic abnormalities such as anemia, thrombocytopenia, and leukopenia.

Second-generation protease inhibitors
The second-generation protease inhibitor simeprevir has demonstrated superior SVR compared with standard regimens of IFN/RBV. In pooled analysis of 2 similar trials, the SVR was 80%, and in a third trial the SVR was 79%. AEs occurred at rates higher than placebo for skin reactions, hyperbilirubinemia, and dyspnea. Compared with first-generation protease inhibitors, response rates for simeprevir may be higher and AEs rates lower; however, direct comparisons on the 2 medications are not available.

**NS5B RNA polymerase inhibitors**

Sofosbuvir is currently the only FDA-approved NS5B RNA polymerase inhibitor. The evidence on this medication comes from a mix of randomized and nonrandomized trials, some of which have yet to be published. The range of SVR12 in these studies is from 67% to 97%, with several trials reporting SVR rates that are higher than with other DAAs. The safety profile of sofosbuvir is favorable compared with other DAAs. However, there are no direct comparisons of sofosbuvir to other DAAs. SAEs were uncommon in the trials, and serious hematologic abnormalities occurred in 4% or less of patients.

**Combination medications**

On October 10, 2014, ledipasvir/sofosbuvir became the first combination treatment to receive FDA approval. Results from the trials of this drug report very high response rates, in the range of 94% to 99%

There is no direct evidence comparing outcomes of immediate versus delayed treatment with DAAs. However, the degree of treatment benefit, and the implications of delaying treatment, can be inferred from knowledge of the natural history of hepatitis C. The long interval between chronic hepatitis C infection and the development of irreversible cirrhosis implies that patients will not be harmed by delay of treatment if they have early disease, if treatment is initiated before the development of irreversible liver damage. For patients with cirrhosis, or at high risk for progression to cirrhosis in the near future, immediate treatment is indicated, and delay of treatment may result in worse outcomes. Other patients who should be treated without delay include those with serious extrahepatic manifestations of hepatitis C, and those with HCC awaiting transplant.

**Summary**

The availability of direct acting antiviral (DAAs) represents a major advancement in the treatment of hepatitis C, with the potential to dramatically improve cure rates with less toxicity compared with standard treatment without DAAs. All of the DAAs that are currently U.S. Food and Drug Administration approved have demonstrated treatment responses that are superior to standard care consisting of interferon and ribavirin. Direct comparisons of the different agents are lacking, but differences in treatment response and adverse effects are reported. The first-generation protease inhibitors, boceprevir and telaprevir, have response rates in the 60% to 80% range and a relatively high incidence of serious adverse effects. The second-generation protease inhibitor, simeprevir offers an improved risk/benefit ratio, and treatment with the RNA polymerase inhibitor sofosbuvir has resulted in higher response rates and less toxicity than any of the other available agents.
There is no direct evidence on immediate versus delayed treatment, but based on the natural history of the disease, it is reasonable to conclude that some patients can have treatment delayed without suffering adverse outcomes. These are generally patients with no fibrosis or early fibrosis. Outcomes will not be adversely impacted if these patients have close monitoring and if treatment is instituted prior to the onset of irreversible liver damage. For patients with more advanced disease, immediate treatment should be given to avoid progression of irreversible liver damage. Other patients that should be treated without delay include patients with serious extrahepatic manifestations of hepatitis C and patients with hepatocellular carcinoma awaiting transplant.

Based on the available evidence, treatment with DAAs for patients with chronic hepatitis C infection may be considered medically necessary. For patients with early disease, either immediate or delayed treatment may be considered medically necessary. For patients with advanced disease, patients with serious extrahepatic manifestations, and patients with hepatocellular carcinoma awaiting transplant, only immediate treatment may be considered medically necessary.

Various professional societies, governmental agencies and health plans have developed policies and treatment regimens for HCV. Those of the Department of Veterans Affairs, American Association for the Study of Liver Diseases, American College of Gastroenterology and others can be found in the References section.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.
VII. References


### Appendix A

**Meta-analysis of Histological Data in Viral Hepatitis (METAVIR)**

<table>
<thead>
<tr>
<th>METAVIR Fibrosis Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>1</td>
<td>Portal fibrosis without septa (bridges)</td>
</tr>
<tr>
<td>2</td>
<td>Portal fibrosis with septa (bridges)</td>
</tr>
<tr>
<td>3</td>
<td>Numerous septa without cirrhosis</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>
Appendix B

Milan Criteria
The Milan criteria are a generally accepted set of criteria to assess suitability in patients with cirrhosis and hepatocellular carcinoma for liver transplantation.

According to the Milan criteria, in order to be suitable for liver transplantation one needs to have:
- no lesion larger than 5 cm
- ≤ 3 lesions with diameter ≤ 3 cm
- no extrahepatic involvement
- no major vessel involvement
Appendix C

FDA-Approved Treatment Regimen

The recommended dose of Harvoni is one tablet (90 mg of ledipasvir and 400 mg of sofosbuvir), taken orally, daily with or without food. The recommended regimen and treatment duration for Harvoni is provided in Table 1.

Table 1  Recommended Regimens and Treatment Duration for Harvoni

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Recommended Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve with or without cirrhosis</td>
<td>12 weeks*</td>
</tr>
<tr>
<td>Treatment-experienced** without cirrhosis</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Treatment-experienced** with cirrhosis</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

*  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.

**  Treatment-experienced patients who have failed treatment with either peginterferon alfa + ribavirin or an HCV protease inhibitor + peginterferon alfa + ribavirin.
Appendix D

Child-Pugh Score
The Child-Pugh Score, also known as Child-Turcotte-Pugh score, is a scoring system for severity of liver disease and likelihood of survival based on the presence of degenerative disease of the brain (encephalopathy), the escape or accumulation of fluid in the abdominal cavity (ascites), laboratory measures of various substances in the blood (see table below), and the presence of other co-existing diseases; after calculating the CTP score using a table similar to the one below, individuals can be classified into one of three categories:

- Childs A (5-6 points): 10 year survival 80-90%
- Childs B (7-9 points): 5 year survival 60-80%; and
- Childs C (10-15 points): 2 year survival less than 50%

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>Greater than 3.5</td>
<td>2.8 – 3.5</td>
<td>Less than 2.8</td>
</tr>
<tr>
<td>Prothrombin time (International Normalized ratio) prolonged</td>
<td>Less than 4</td>
<td>4 – 6</td>
<td>Greater than 6</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1 - 4</td>
<td>4 – 10</td>
<td>Greater than 10</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis/primary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other diseases</td>
<td>Less than 2</td>
<td>1 – 3</td>
<td>Greater than 3</td>
</tr>
</tbody>
</table>

Compensated liver disease: Child-Pugh score less than or equal to 6 (class A) in cirrhotic individuals before or during treatment.

Decompensated liver disease: Child-Pugh score greater than 6 (class B or class C) in cirrhotic individuals before or during treatment.
Appendix E

HMSA Hepatitis C Treatment Checklist

<table>
<thead>
<tr>
<th>HMSA HEPATITIS C TREATMENT CHECKLIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage of ledipasvir/sofosbuvir (Harvoni) for the treatment of Hepatitis C is covered only if you meet HMSA policies and guidelines related to the treatment. You must comply with all instructions given to you by your physician and pharmacy, and agree to avoid all activities that may worsen your liver disease or infect yourself or others with the hepatitis C virus or other bloodborne pathogens. By initialing 1 through 9 and signing below where indicated you promise to comply with the requirements of this checklist.</td>
</tr>
</tbody>
</table>

Please initial in the space provided next to each statement below. By initialing you agree to comply with each statement.

| 1. | I agree to comply with all instructions from my physician and dispensing pharmacy related to the medication prescribed and dispensed to me. |
| 2. | I agree to keep all appointments scheduled with my physician. |
| 3. | I agree to not use alcohol or illicit drugs for the 6 months preceding and during treatment for hepatitis C. |
| 4. | I agree to attend Alcoholics Anonymous (AA), Narcotics Anonymous (NA) or a similar program for substance abuse, if recommended by my physician. |
| 5. | I agree to use only the medications prescribed by my physician. |
| 6. | I agree to random drug and alcohol testing, if requested by my physician. |
| 7. | I agree to routine blood testing for the hepatitis C virus when ordered by my physician. |
| 8. | I understand that this treatment for hepatitis C is intended to be a once per lifetime treatment. |
| 9. | I understand that extreme caution must be taken to avoid pregnancy in female patients and in female partners of male patients. As such, I will use contraception to avoid pregnancy if I am sexually active and I or my partner are of child-bearing age. |

By signing below I am indicating that I will comply with 1 through 9 above. I have had an opportunity to ask questions about this form and my questions have been answered to my satisfaction. I understand that payment by HMSA of the medication prescribed by my physician to treat hepatitis C is dependent upon my compliance with the statements above. I further understand that HMSA will discontinue payment for treatment with my medication to treat hepatitis C if at any time I am not
compliant with 1 through 9 above. I further understand that HMSA will not pay to replace the medication prescribed if the medication is lost, stolen, destroyed or otherwise not available to me.

Patient Name: __________________________

Patient Signature: ______________________

Date: __________________________