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 one to three weeks after exposure, and anti-HCV seroconversion occurs by eight to nine weeks after exposure.

Progression of chronic hepatitis C infection to end stage liver disease most commonly occurs over several decades. Early in the course of infection, serum or liver-related enzyme levels, such as alanine aminotransferase, aspartate aminotransferase, and y-glutamyltranspeptidase 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. However, many patients may go decades or a lifetime without substantial liver 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 co-factors such as alcohol consumption, diabetes mellitus, older age at acquisition, HIV co-infection, and co-infection with other hepatic viruses.

An assessment of the severity of hepatic fibrosis is important for treatment and prognosis of chronic HCV infection. A variety of fibrosis scoring systems are available that gauge the degree of hepatic fibrosis with either direct observation of fibrosis through liver biopsy or noninvasive measurement of a biological correlate of hepatic fibrosis (see Appendix A). The METAVIR fibrosis scoring system is the most commonly used method to stage and grade hepatic fibrosis and it assigns a score from F0 to F4 based on a liver biopsy. Several blood tests that detect serological markers of hepatic fibrosis also produce scores that can be staged to estimate degree of fibrosis (e.g., HepaScore, FibroSure, FibroSpect II). Another group of tests involve radiological imaging to measure qualities about the liver without an invasive surgery; these
include magnetic resonance elastography (MRE), ultrasound transient elastography (e.g., FibroScan), and acoustic radiation force impulse imaging (ARFI; e.g., Acuson S2000).

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 to treatment regimens that do not include DAAs.

### Direct Acting Antiviral Medications for Treatment of Hepatitis C

#### HMSA QUEST Formulary and Non-Formulary Drugs

<table>
<thead>
<tr>
<th>Quest</th>
<th>Genotype 1</th>
<th>Genotype 2</th>
<th>Genotype 3</th>
<th>Genotype 4</th>
<th>Genotype 5,6</th>
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<tbody>
<tr>
<td>On formulary</td>
<td>Harvoni</td>
<td>Epclusa</td>
<td>Epclusa</td>
<td>Harvoni</td>
<td>Harvoni</td>
</tr>
<tr>
<td></td>
<td>Zepatier</td>
<td></td>
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<tr>
<td></td>
<td>Sovaldi</td>
<td></td>
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</tr>
<tr>
<td>Non-formulary</td>
<td>Daklinza</td>
<td></td>
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<tr>
<td></td>
<td>Olysio</td>
<td></td>
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<td></td>
<td>Technivie</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Viekira Pak/XR</td>
<td></td>
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</tbody>
</table>

#### HMSA HMO PPO Preferred and Non-Preferred Drugs

<table>
<thead>
<tr>
<th>PPO HMO</th>
<th>Genotype 1</th>
<th>Genotype 2</th>
<th>Genotype 3</th>
<th>Genotype 4</th>
<th>Genotype 5,6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>Harvoni</td>
<td>Epclusa</td>
<td>Epclusa</td>
<td>Harvoni</td>
<td>Harvoni</td>
</tr>
<tr>
<td></td>
<td>Sovaldi</td>
<td></td>
<td></td>
<td>Sovaldi</td>
<td></td>
</tr>
<tr>
<td>Non-preferred/ Non-formulary</td>
<td>Daklinza</td>
<td></td>
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<tr>
<td></td>
<td>Olysio</td>
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<td></td>
<td>Viekira Pak/XR</td>
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<td></td>
<td>Zepatier</td>
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</table>

### Prioritizing Patients to Receive Treatment for Chronic Hepatitis C

The combined American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidelines for the treatment of chronic hepatitis C are available at [http://www.hcvguidelines.org/](http://www.hcvguidelines.org/). These guidelines are updated frequently, so providers should check them periodically for the most up to date recommendations on patient care. The recommendations in these guidelines are a valuable resource for this policy but do not
alone form a basis for approval of a particular course of treatment. To ensure that patients with the greatest need receive treatment, patients must be prioritized so that those with at least portal fibrosis, liver-related complications or severe extrahepatic hepatitis C complications are given the highest priority for treatment.

II. General Criteria/Guidelines

A. DAA medications are 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 prescribing physician attests that the patient is at low risk for noncompliance with the treatment regimen
   3. The patient has an HCV RNA positive diagnosis documented by a quantitative titer
   4. The patient has no history of alcohol or substance abuse within the six months prior to treatment initiation
   5. The patient presents with at least one of the following indications:
      a. Liver biopsy with a METAVIR stage of F1, F2, F3 or F4 (refer to Appendix A);
      b. Transient elastography (FibroScan) score greater than or equal to 5.3 kPa;
      c. FibroSure (FibroTest) score of greater than or equal to 0.27;
      d. Score from another blood test that detects serological markers of hepatic fibrosis that is equivalent to a METAVIR stage of F1, F2, F3 or F4 (refer to Appendix A);
      e. Radiological imaging consistent with cirrhosis (e.g., evidence of portal hypertension);
      f. Clinical findings consistent with cirrhosis (i.e., ascites or esophageal varices);
      g. Serious extrahepatic manifestations of hepatitis C, i.e., type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (e.g., vasculitis), proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
      h. Organ transplant; or
      i. HIV co-infection
   6. The medication is being prescribed by, or in consultation with, one of the following specialists:
      a. Hepatologist;
      b. Gastroenterologist;
      c. Infectious Disease Specialist; or
      d. HIV Specialist
   7. 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 use during the course of treatment;
      d. Drug testing, when recommended by the treating provider; and
      e. Blood draws to measure HCV RNA, when ordered.
   8. Treatment is in accordance with FDA approved treatment regimens unless otherwise noted in drug-specific criteria/guidelines (refer to Drug-Specific Criteria/Guidelines)

B. DAA medications are 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.1-4, 6-8) 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.

C. Patients who experienced prior treatment failure may be treated as outlined in the drug-specific criteria/guidelines within Criteria for Approval section for specific genotype (refer to Drug-Specific Criteria/Guidelines).

III. Formulary/Preferred Drug Requirements

A. For QUEST members, the following DAAs are on-formulary options: Harvoni (genotype 1, 4, 5 or 6), Sovaldi (genotype 1 or 4), Zepatier (genotype 1 or 4) and Epclusa (genotype 2 or 3).

B. For PPO/HMO members, the following DAAs are preferred options: Harvoni (genotype 1, 4, 5 or 6), Sovaldi (genotype 1 or 4), and Epclusa (genotype 2 or 3).

C. Requests for non-formulary/non-preferred DAAs will be considered in the following situations:
   1. Member had an inadequate treatment response with a formulary/preferred option (see IV.D. below)
   2. Member has a contraindication to a formulary/preferred option
      Note: members with end-stage renal disease or severe renal impairment (creatinine clearance less than 30 mL/min) may receive Zepatier as an alternative to Harvoni or Sovaldi where applicable
   3. Member has a history of intolerance or an adverse event due to previous treatment with a formulary/preferred option

D. Formulary/preferred drug exceptions criteria are not required for members who are continuing a course of treatment with the requested non-formulary/non-preferred DAA medication.

IV. Limitations

A. Treatment of HCV with DAA medication is not covered when any of the general criteria and formulary/preferred drug requirements specified above (Sections II and III) are not met.

B. Treatment of HCV with DAA medication is not covered for patients with short life expectancies due to comorbid conditions.

C. Treatment is contraindicated in patients with a known hypersensitivity or allergy to the prescribed drug used to treat hepatitis C.

D. Repeat treatments in any of the following situations will 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; or
   4. A prior treatment failure when there is no recognized, effective retreatment regimen.

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

V. Dosage and Administration
A. Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

B. A 28-day supply dispense limit applies to all targeted hepatitis C agents in order to better manage the therapy regimen.

VI. Administrative Guidelines

Prior authorization is required. To preauthorize Hep C therapy, contact CVS Specialty Guideline Management (SGM) at (808) 254-4414.

A. The following medical record documentation, as applicable to the patient, must be submitted with the prior authorization request:
   1. Written treatment plan from the requesting provider
   2. Documentation that the member has been assessed for potential non-adherence to treatment regimen
   3. HCV RNA laboratory report with viral load and genotype
   4. Documentation of test/procedure results performed to assess hepatic fibrosis (eg, liver biopsy) or complications (eg, ascites)
   5. Laboratory testing for resistance associated variants (RAVs) (refer to drug-specific criteria for details)
      a. Harvoni and Epclusa: NS5A inhibitor RAVs where applicable
      b. Olysio: NS3 Q80K polymorphism, NS5A inhibitor RAVs, or NS3 protease inhibitor RAVs where applicable
      c. Zepatier for genotype 1a: baseline NS5A polymorphisms

B. A specialty pharmacy will dispense no more than 28 days of medication at one time.

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

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

VII. Appendix

Appendix A

Meta-analysis of Histological Data in Viral Hepatitis

<table>
<thead>
<tr>
<th>Table 1: METAVIR Fibrosis Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>


FibroSure Score Ranges
Table 2: Comparison Between FibroSure Score and METAVIR Stage

<table>
<thead>
<tr>
<th>FibroSure Score</th>
<th>METAVIR Stage Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.21</td>
<td>Stage F0</td>
</tr>
<tr>
<td>0.21 – 0.27</td>
<td>Stage F0 – F1</td>
</tr>
<tr>
<td>0.27 – 0.31</td>
<td>Stage F1</td>
</tr>
<tr>
<td>0.31 – 0.48</td>
<td>Stage F1 – F2</td>
</tr>
<tr>
<td>0.48 – 0.58</td>
<td>Stage F2</td>
</tr>
<tr>
<td>0.58 – 0.72</td>
<td>Stage F3</td>
</tr>
<tr>
<td>0.72 – 0.74</td>
<td>Stage F3 – F4</td>
</tr>
<tr>
<td>&gt; 0.74</td>
<td>Stage F4</td>
</tr>
</tbody>
</table>


Transient Elastography Cutoff Values

Table 3: Comparison Between FibroScan Measurement and METAVIR Stage

<table>
<thead>
<tr>
<th>FibroScan Measurement (kPa)</th>
<th>METAVIR Stage Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.0</td>
<td>Stage F2</td>
</tr>
<tr>
<td>9.5</td>
<td>Stage F3</td>
</tr>
<tr>
<td>11.8</td>
<td>Stage F4</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

VIII. Drug-Specific Criteria/Guideline

Drug specific criteria begin on page 8.
Appendix C

HMSA Hepatitis C Treatment Checklist

<table>
<thead>
<tr>
<th>HMSA HEPATITIS C TREATMENT CHECKLIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage of Direct Acting Antiviral medications 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 8 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. |

By signing below I am indicating that I will comply with 1 through 8 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 8 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: ___________________________
HARVONI
(ledipasvir and sofosbuvir)

I. INDICATIONS

FDA-Approved Indications
Harvoni is indicated with or without ribavirin for the treatment of patients with chronic hepatitis C virus (HCV) genotype 1, 4, 5 or 6 infection.

II. EXCLUSIONS
Use with other drugs containing sofosbuvir, including Sovaldi

Note: When the requested drug is being used in a combination therapy regimen, exclusions to the other antiviral drugs also apply.

III. CRITERIA FOR APPROVAL
1. Chronic hepatitis C virus infection, without ribavirin
   1.1 Genotype 1 infection
      a. Authorization of up to 12 weeks total may be granted for treatment-naïve members with compensated cirrhosis.
      b. Authorization of up to 8 weeks total may be granted for treatment-naive members without cirrhosis who have pre-treatment HCV RNA below 6 million IU/mL.
      c. Authorization of up to 12 weeks may be granted for treatment-naive members without cirrhosis who have pre-treatment HCV RNA greater than or equal to 6 million IU/mL or HIV co-infection.
      d. Authorization of up to 12 weeks total may be granted for members without cirrhosis who failed prior treatment with peginterferon alfa (PEG-IFN) and ribavirin (RBV) with or without an HCV protease inhibitor.
      e. Authorization of up to 24 weeks total may be granted for members with compensated cirrhosis who failed prior treatment with PEG-IFN and RBV with or without an HCV protease inhibitor.

   1.2 Genotype 4 infection
      a. Authorization of up to 12 weeks total may be granted for treatment-naïve members without cirrhosis or with compensated cirrhosis.
      b. Authorization of up to 12 weeks total may be granted for members without cirrhosis who failed prior treatment with PEG-IFN and RBV with or without an HCV protease inhibitor.
      c. Authorization of up to 24 weeks total may be granted for members with compensated cirrhosis who failed prior treatment with PEG-IFN and RBV with or without an HCV protease inhibitor.

   1.3 Genotype 5 infection
Authorization of up to 12 weeks total may be granted for members who are treatment-naive or who failed prior treatment with PEG-IFN and RBV with or without an HCV protease inhibitor.

### 1.4 Genotype 6 infection
Authorization of up to 12 weeks total may be granted for members who are treatment-naive or who failed prior treatment with PEG-IFN and RBV with or without an HCV protease inhibitor.

### 1.5 Decompensated cirrhosis (CTP class B or C)
Authorization of up to 24 weeks total may be granted for members with HCV genotype 1 or 4 infection and documented anemia (baseline Hgb below 10 g/dL) or RBV ineligibility (see Section IV).

### 1.6 Recurrent HCV infection post liver transplantation
Authorization of up to 24 weeks total may be granted for treatment-naive members who have recurrent HCV genotype 1 or 4 infection post liver transplantation and documented anemia (baseline Hgb below 10 g/dL) or RBV ineligibility (see Section IV).

### 2. Chronic hepatitis C virus infection, in combination with ribavirin

#### 2.1 Genotype 1 infection
- a. Authorization of up to 12 weeks total may be granted for members with compensated cirrhosis who failed prior treatment with PEG-IFN and RBV with or without an HCV protease inhibitor.
- b. Authorization of up to 12 weeks total may be granted for members without cirrhosis who failed prior treatment with sofosbuvir plus RBV with or without PEG-IFN.
- c. Authorization of up to 24 weeks total may be granted for members with compensated cirrhosis who failed prior treatment with sofosbuvir plus RBV with or without PEG-IFN.
- d. Authorization of up to 24 weeks total may be granted for members with compensated cirrhosis who failed prior treatment with sofosbuvir plus simeprevir with or without RBV and do not have any NS5A resistance-associated variants (RAVs) associated with ledipasvir resistance.
- e. Authorization of up to 24 weeks total may be granted for members with compensated cirrhosis who failed prior treatment with an HCV NS5A inhibitor and do not have any NS5A RAVs associated with ledipasvir resistance.

#### 2.2 Genotype 4 infection
Authorization of up to 12 weeks total may be granted for members with compensated cirrhosis who failed prior treatment with PEG-IFN and RBV with or without an HCV protease inhibitor.

#### 2.3 Decompensated cirrhosis (CTP class B or C)
- a. Authorization of up to 12 weeks total may be granted for members with HCV genotype 1 or 4 infection.
b. Authorization of up to 24 weeks total may be granted for members with HCV genotype 1 or 4 infection who failed prior treatment with a sofosbuvir-containing regimen (e.g., sofosbuvir and RBV, sofosbuvir plus PEG-IFN and RBV, sofosbuvir plus simeprevir with or without RBV).

c. Authorization of up to 12 weeks total may be granted for members with recurrent HCV genotype 1 or 4 infection post liver transplantation and who have decompensated cirrhosis.

2.4 Recurrent HCV infection post liver transplantation

Authorization of up to 12 weeks total may be granted for members with recurrent HCV genotype 1 or 4 infection post liver transplantation.

3. HCV and HIV coinfection

Authorization may be granted for members who meet all of the following criteria:

a. Member meets the criteria for approval for the requested regimen above.

b. Member will not receive treatment with cobicistat given with tenofovir disoproxil fumarate.

c. Member will not receive treatment with tipranavir.

IV. APPENDIX

RIBAVIRIN INELIGIBILITY

RBV ineligibility is defined as one or more of the below:

A. Intolerance to RBV
B. Pregnant female or male whose female partner is pregnant
C. Hemoglobinopathy
D. Coadministration with didanosine
VIEKIRA PAK
VIEKIRA XR
(ombitasvir/paritaprevir/ritonavir with dasabuvir)

I. INDICATIONS

FDA-Approved Indications
Viekira Pak with or without ribavirin is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.

II. EXCLUSIONS

A. Decompensated cirrhosis/moderate or severe hepatic impairment (Child Turcotte Pugh Class B or C)
B. Concomitant use with drugs that are highly dependent on CYP3A for clearance, moderate or strong inducers of CYP3A, strong inducers of CYP2C8, or strong inhibitors of CYP2C8 (See Section IV)
C. Prior treatment failure with an HCV protease inhibitor (eg, telaprevir, boceprevir, simeprevir, paritaprevir) despite adequate dosing and duration of therapy

Note: When the requested drug is being used in a combination therapy regimen, exclusions to the other antiviral drugs also apply.

III. CRITERIA FOR APPROVAL

1. Chronic hepatitis C virus infection, in combination with ribavirin (RBV)

Note: Members with mixed genotype 1 infection or unknown genotype 1 subtype should follow the criteria for approval for genotype 1a infection.

1.1 Genotype 1a infection

   a. Authorization of up to 12 weeks total may be granted for members without cirrhosis who meet one of the following criteria:
      i. Treatment-naïve
      ii. Failed prior treatment with peginterferon alfa (PEG-IFN) and RBV.

   b. Authorization of up to 24 weeks total may be granted for members with cirrhosis who meet one of the following criteria:
      i. Treatment-naïve
      ii. Failed prior treatment with PEG-IFN and RBV.

1.2 Genotype 1b infection

   Authorization of up to 12 weeks total may be granted for members with cirrhosis who meet one of the following criteria:

   a. Treatment-naïve
   b. Failed prior treatment with PEG-IFN and RBV
1.3 Recurrent HCV infection post liver transplantation
Authorization of up to 24 weeks total may be granted for members with recurrent HCV infection post liver transplantation who meet all of the following criteria:
   a. Genotype 1 infection (irrespective of subtype)
   b. Metavir fibrosis score of 2 or lower.

2. Chronic hepatitis C virus infection, without RBV
   Genotype 1b infection
Authorization of up to 12 weeks total may be granted for members with or without cirrhosis who meet one of the following criteria:
   a. Treatment-naïve
   b. Failed prior treatment with PEG-IFN and RBV

3. HCV and HIV coinfection
Authorization may be granted for members who meet all of the following criteria:
   a. Member meets the criteria for approval for the requested regimen above.
   b. Member is currently receiving antiretroviral therapy.
   c. Member will not receive treatment with darunavir, efavirenz, ritonavir-boosted lopinavir, rilpivirine, atazanavir or ritonavir-boosted atazanavir.

IV. APPENDIX: DRUGS THAT ARE CONTRAINDICATED WITH VIEKIRA PAK
   A. alfuzosin
   B. colchicine
   C. carbamazepine
   D. phenytoin
   E. phenobarbital
   F. gemfibrozil
   G. rifampin
   H. ergot derivatives (ergotamine, dihydroergotamine, ergonovine, methylergonovine)
   I. ethinyl estradiol-containing medications (eg, Lo Loestrin Fe, Ortho Tri-Cyclen Lo, Ortho Evra, NuvaRing)
   J. St. John’s wort
   K. lovastatin
   L. simvastatin
   M. pimozone
   N. efavirenz
   O. sildenafil or Revatio when used for the treatment of pulmonary arterial hypertension (PAH)
   P. triazolam
   Q. midazolam, oral
SOVALDI (sofosbuvir)

I. INDICATIONS

FDA-Approved Indications
Sofosbuvir is indicated for the treatment of genotype 1, 2, 3 or 4 chronic hepatitis C virus (HCV) infection as a component of a combination antiviral treatment regimen.

Compendial Uses
Chronic hepatitis C genotype 5 or 6 infection

II. EXCLUSIONS

Prior treatment failure with an HCV protease inhibitor (e.g., telaprevir, simeprevir, boceprevir, paritaprevir) despite adequate dosing and duration of therapy for members prescribed a treatment regimen that includes Olysio.

Note: When the requested drug is being used in a combination therapy regimen, exclusions to the other antiviral drugs also apply.

III. CRITERIA FOR APPROVAL

1. Chronic hepatitis C virus infection, in combination with peginterferon alfa (PEG-IFN) and ribavirin (RBV)
   1.1 Genotype 1 infection
       Authorization of up to 12 weeks total may be granted for members who are treatment-naive or who failed prior treatment with PEG-IFN and RBV.
   1.2 Genotype 2 infection
       a. Authorization of up to 12 weeks total may be granted for members who failed prior treatment with PEG-IFN and RBV.
       b. Authorization of up to 12 weeks total may be granted for members who failed prior treatment with sofosbuvir and ribavirin.
   1.3 Genotype 3, 4, 5, 6 infection
       Authorization of up to 12 weeks total may be granted for members who are treatment-naive or who failed prior treatment with PEG-IFN and RBV. Authorization of up to 12 weeks total may also be granted for members with genotype 3 infection who failed prior treatment with sofosbuvir and RBV.

2. Chronic hepatitis C virus infection, in combination with RBV
   2.1 Genotype 1 infection
       Authorization of up to 24 weeks total may be granted for members who have documented interferon (IFN) ineligibility (see Section IV).
   2.2 Genotype 2 infection
       a. Authorization of up to 12 weeks total may be granted for members without cirrhosis who are treatment-naive.
b. Authorization of up to 16 weeks total may be granted for members with cirrhosis who are treatment-naïve.
c. Authorization of up to 16 weeks total may be granted for members without cirrhosis who failed prior treatment with PEG-IFN and RBV
d. Authorization of up to 24 weeks total may be granted for members with cirrhosis who failed prior treatment with PEG-IFN and RBV.

2.3 Genotype 3 infection
Authorization of up to 24 weeks total may be granted for members with documented IFN ineligibility who are treatment-naïve.

2.4 Genotype 4 infection
Authorization of up to 24 weeks total may be granted for members who are treatment-naïve or who failed prior treatment with PEG-IFN and RBV.

2.5 Members with hepatocellular carcinoma awaiting liver transplantation
Authorization of up to 48 weeks total or until liver transplantation, whichever occurs first, may be granted for members with genotype 1, 2, 3, or 4 infection and hepatocellular carcinoma who meet the MILAN criteria, defined as the following:
   a. Tumor size 5 cm or less in diameter with single hepatocellular carcinomas OR 3 tumor nodules or less, each 3 cm or less in diameter with multiple tumors AND
   b. No extrahepatic manifestations of the cancer or evidence of vascular invasion of tumor

2.6 Recurrent HCV infection post liver transplantation
Authorization of up to 24 weeks total may be granted for members with recurrent HCV genotype 2 or 3 infection post liver transplantation.

2.7 Decompensated cirrhosis (Child Turcotte Pugh [CTP] class B or C)
Authorization of up to 48 weeks total may be granted for members with genotype 2 or 3 infection and decompensated cirrhosis.

3. Chronic hepatitis C virus infection, in combination with Olysio (with or without RBV)
Authorization of up to 24 weeks total (as applicable) may be granted for members prescribed Sovaldi in combination with Olysio (with or without ribavirin as applicable) who meet the criteria for approval for the requested regimen. Refer to the Olysio section of this policy for the specific criteria for approval and approval durations.

4. Chronic hepatitis C virus infection, in combination with Daklinza (with or without ribavirin)
Authorization of up to 24 weeks total (as applicable) may be granted for members prescribed Sovaldi in combination with Daklinza (with or without ribavirin as applicable) who meet the criteria for approval for the requested regimen. Refer to the Daklinza section of this policy for the specific criteria for approval and approval durations.

5. HCV and HIV coinfection
Authorization may be granted for members who meet all of the following criteria:
   a. Member meets the criteria for approval for the requested regimen above.
   b. Member will not receive treatment with tipranavir.
IV. **APPENDIX**

**INTERFERON INELIGIBILITY**

IFN ineligible is defined as one or more of the below:

- A. Intolerance to IFN
- B. Autoimmune hepatitis and other autoimmune disorders
- C. Hypersensitivity to PEG-IFN or any of its components
- D. Major uncontrolled depressive illness
- E. A baseline neutrophil count < 1,500/mcL
- F. A baseline platelet count < 90,000/mcL
- G. A baseline hemoglobin < 10 g/dL
- H. History of pre-existing cardiac disease
DAKLINZA (daclatasvir)

I. INDICATIONS

FDA-Approved Indication

Daklinza is indicated for use with sofosbuvir for the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infection.

Limitations of Use:

Sustained virologic response (SVR) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving Daklinza in combination with sofosbuvir for 12 weeks.

Compendial Uses

Chronic hepatitis C genotype 1, 2, or 4 infection

II. EXCLUSIONS

Use with a strong inducer of CYP3A, including phenytoin, carbamazepine, rifampin and St. John’s wort

Note: When the requested drug is being used in a combination therapy regimen, exclusions to the other antiviral drugs also apply.

III. CRITERIA FOR APPROVAL

1. Chronic hepatitis C virus infection, in combination with Sovaldi
   1.1 Genotype 1 infection
      a. Authorization of up to 12 weeks total may be granted for treatment-naive members without cirrhosis.
      b. Authorization of up to 12 weeks total may be granted for members without cirrhosis who failed prior treatment with PEG-IFN and RBV with or without an HCV protease inhibitor.
      c. Authorization of up to 24 weeks total may be granted for treatment-naive members with cirrhosis.
      d. Authorization of up to 24 weeks total may be granted for members with cirrhosis who failed prior treatment with PEG-IFN and RBV with or without an HCV protease inhibitor.
   1.2 Genotype 2 infection
      a. Authorization of up to 12 weeks total may be granted for treatment-naive members with documented anemia (baseline hemoglobin [Hgb] below 10 g/dL) or RBV ineligibility (see Section IV).
      b. Authorization of up to 24 weeks total may be granted for members who failed prior treatment with sofosbuvir and ribavirin and have documented interferon (IFN) ineligibility (see Section IV).
1.3 **Genotype 3 infection**
   a. Authorization of up to 12 weeks total may be granted for treatment-naive members without cirrhosis.
   b. Authorization of up to 12 weeks total may be granted for members with or without cirrhosis who failed prior treatment with peginterferon alfa (PEG-IFN) and ribavirin (RBV).
   c. Authorization of up to 24 weeks total may be granted for treatment-naive members with cirrhosis.
   d. Authorization of up to 12 weeks total may be granted for members with or without cirrhosis who failed prior treatment with a sofosbuvir-based regimen.

1.4 **Decompensated cirrhosis (Child Turcotte Pugh [CTP] class B or C)**
   Authorization of up to 24 weeks total may be granted for members with HCV genotype 1 or 4 infection and documented anemia (baseline hemoglobin [Hgb] below 10 g/dL) or RBV ineligibility (see Section IV).

1.5 **Recurrent HCV infection post liver transplantation**
   a. Authorization of up to 24 weeks total may be granted for treatment-naive members who have recurrent HCV genotype 1, 3 or 4 infection post liver transplantation and documented anemia (baseline Hgb below 10 g/dL) or RBV ineligibility (see Section IV).
   b. Authorization of up to 24 weeks total may be granted for members who have recurrent HCV genotype 2 infection post liver transplantation and documented anemia (baseline Hgb below 10 g/dL) or RBV ineligibility (see Section IV).

2. **Chronic hepatitis C virus, in combination with Sovaldi and RBV**
   2.1 **Genotype 1 infection**
      a. Authorization of up to 24 weeks total may be granted for treatment-naive members with cirrhosis.
      b. Authorization of up to 24 weeks total may be granted for members with cirrhosis who failed prior treatment with PEG-IFN and RBV with or without an HCV protease inhibitor.

   2.2 **Genotype 2 infection**
      Authorization of up to 24 weeks total may be granted for members who failed prior treatment with sofosbuvir and ribavirin and have documented interferon (IFN) ineligibility (see Section IV).

   2.3 **Genotype 3 infection**
      a. Authorization of up to 24 weeks total may be granted for treatment-naive members with cirrhosis.
      b. Authorization of up to 24 weeks total may be granted for members with cirrhosis who failed prior treatment with PEG-IFN and RBV and have documented IFN ineligibility (see Section IV).
c. Authorization of up to 24 weeks total may be granted for members who failed prior treatment with sofosbuvir and RBV and have documented IFN ineligibility (see Section IV).

2.4 Decompensated cirrhosis (CTP class B or C)

Authorization of up to 12 weeks total may be granted for members with HCV genotype 1, 2, 3 or 4 infection.

2.5 Recurrent HCV infection post liver transplantation

Authorization of up to 12 weeks total may be granted for members with recurrent HCV genotype 1, 2, 3 or 4 infection post liver transplantation.

3. HCV and HIV coinfection

Authorization may be granted for members who meet the criteria for approval for the requested regimen above.

IV. APPENDICES

RIBAVIRIN INELIGIBILITY

RBV ineligibility is defined as one or more of the below:
A. Intolerance to RBV
B. Pregnant female or male whose female partner is pregnant
C. Hemoglobinopathy
D. Coadministration with didanosine

INTERFERON INELIGIBILITY

IFN ineligible is defined as one or more of the below:
A. Intolerance to IFN
B. Autoimmune hepatitis and other autoimmune disorders
C. Hypersensitivity to PEG-IFN or any of its components
D. Major uncontrolled depressive illness
E. A baseline neutrophil count < 1,500/mcL
F. A baseline platelet count < 90,000/mcL
G. A baseline hemoglobin < 10 g/dL
H. History of pre-existing cardiac disease
I. INDICATIONS

FDA-Approved Indications
Technivie is indicated in combination with ribavirin for the treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection without cirrhosis.

II. EXCLUSIONS
A. Decompensated cirrhosis/moderate or severe hepatic impairment (Child Turcotte Pugh Class B or C)
B. Concomitant use with drugs that are highly dependent on CYP3A for clearance (See Section IV)
C. Concomitant use with drugs that are moderate or strong inducers of CYP3A (See Section IV)
D. Prior treatment failure with an HCV protease inhibitor (eg, telaprevir, boceprevir, simeprevir, paritaprevir) despite adequate dosing and duration of therapy

III. CRITERIA FOR APPROVAL
1. Chronic hepatitis C virus infection, in combination with ribavirin (RBV)
   1.4 Genotype 4 infection
   a. Authorization of up to 12 weeks total may be granted for members without cirrhosis who meet one of the following criteria:
      i. Treatment-naïve
      ii. Failed prior treatment with peginterferon alfa and RBV

2. Chronic hepatitis C virus infection, without RBV
   2.1 Genotype 4 infection
   a. Authorization of up to 12 weeks total may be granted for members without cirrhosis who meet all of the following criteria:
      i. Treatment-naïve
      ii. Member has intolerance to RBV, has documented anemia (baseline hemoglobin below 10 g/dL) or RBV ineligibility (see Section V for ribavirin ineligibility)

3. HCV and HIV coinfection
   a. Authorization may be granted for members who meet all of the following criteria:
      i. Member meets the criteria for approval for the requested regimen in Section III above.
      ii. Member is currently receiving antiretroviral therapy
      iii. Member will not receive treatment with darunavir, efavirenz, ritonavir-boosted lopinavir, rilpivirine, atazanavir or ritonavir-boosted atazanavir.
IV. APPENDIX: DRUGS THAT ARE CONTRAINDIATED WITH TECHNIVIE
A. alfuzosin
B. colchicine
C. carbamazepine
D. phenytoin
E. phenobarbital
F. rifampin
G. ergot derivatives (ergotamine, dihydroergotamine, ergonovine, methylergonovine)
H. ethinyl estradiol-containing medications (eg, Lo Loestrin Fe, Ortho Tri-Cyclen Lo, Ortho Evra, NuvaRing)
I. St. John’s wort
J. lovastatin
K. simvastatin
L. pimozide
M. efavirenz
N. sildenafil or Revatio when used for the treatment of pulmonary arterial hypertension (PAH)
O. triazolam
P. midazolam, oral

V. APPENDIX: RIBAVIRIN INELIGIBILITY
RBV ineligibility is defined as one or more of the below:
A. Pregnant female or male whose female partner is pregnant
B. Hemoglobinopathy
C. Coadministration with didanosine
ZEPATIER (elbasvir and grazoprevir)

I. INDICATIONS

FDA-Approved Indications
Zepatier is indicated with or without ribavirin for the treatment of chronic hepatitis C virus genotypes 1 or 4 infection in adults.

II. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions:
A. Decompensated cirrhosis/moderate or severe hepatic impairment (Child Turcotte Pugh Class B or C)
B. Concomitant use with drugs that are organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors (See Section IV)
C. Concomitant use with drugs that are strong inducers of cytochrome P450 3A (CYP3A) and efavirenz (See Section IV)
D. Liver transplant recipient or awaiting liver transplantation

Note: When the requested drug is being used in a combination therapy regimen, exclusions to the other antiviral drugs also apply.

III. CRITERIA FOR APPROVAL

1. Chronic hepatitis C virus infection, in combination with ribavirin (RBV)
   1.1 Genotype 1a infection
   a. Authorization of up to 16 weeks total may be granted for members with baseline NS5A polymorphisms (see Section V) who are either of the following:
      i. Treatment-naïve
      ii. Failed prior treatment with peginterferon alfa (PEG-IFN) and RBV without an HCV protease inhibitor (boceprevir, simeprevir or telaprevir)
   b. Authorization of up to 12 weeks total may be granted for members without baseline NS5A polymorphisms (see Section V) who have failed prior treatment with PEG-IFN and RBV with an HCV protease inhibitor (boceprevir, simeprevir or telaprevir).

   1.2 Genotype 1b infection
   Authorization of up to 12 weeks total may be granted for members who failed prior treatment with PEG-IFN and RBV with an HCV protease inhibitor (boceprevir, simeprevir or telaprevir).

   1.3 Genotype 4 infection
   Authorization of up to 16 weeks total may be granted for members who failed prior treatment with PEG-IFN and RBV.
2. **Chronic hepatitis C virus infection, without RBV**
   
   **2.1 Genotype 1a infection**
   Authorization of up to 12 weeks total may be granted for members without baseline NS5A polymorphisms (see Section V) who are either of the following:
   
   a. Treatment-naïve
   b. Failed prior treatment with PEG-IFN and RBV without an HCV protease inhibitor (boceprevir, simeprevir or telaprevir)
   
   **2.2 Genotype 1b infection**
   Authorization of up to 12 weeks total may be granted for members who are either of the following:
   
   a. Treatment-naïve
   b. Failed prior treatment with PEG-IFN and RBV without an HCV protease inhibitor (boceprevir, simeprevir or telaprevir)
   
   **2.3 Genotype 4 infection**
   Authorization of up to 12 weeks total may be granted for treatment-naïve members.

3. **HCV and HIV coinfection**
   Authorization may be granted for members with HCV and HIV coinfection when the criteria for approval of the requested regimen in Section A or B above are met.

IV. **APPENDIX: DRUGS THAT ARE CONTRAINDICATED WITH ZEPATIER**
   
   A. Phenytoin
   B. Carbamazepine
   C. Rifampin
   D. St. John’s wort
   E. Efavirenz
   F. Atazanavir
   G. Darunavir
   H. Lopinavir
   I. Saquinavir
   J. Tipranavir
   K. Cyclosporine

V. **APPENDIX: NS5A RESISTANCE-ASSOCIATED POLYMORPHISMS**

NS5A resistance-associated polymorphisms at amino acid positions M28, Q30, L31 or Y93. Examples include M28V, Q30H, L31M, and Y93H.
EPCLUSA (sofosbuvir and velpatasvir)

I. INDICATIONS

FDA-Approved Indications
Epclusa is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection:
A. without cirrhosis or with compensated cirrhosis
B. with decompensated cirrhosis for use in combination with ribavirin

II. CRITERIA FOR APPROVAL

1. Chronic hepatitis C virus infection (without ribavirin)
   1.1 Genotype 1 infection
   Authorization of up to 12 weeks total may be granted for members without cirrhosis or with compensated cirrhosis who are treatment-naïve or who failed prior treatment with peginterferon (PEG-IFN) and ribavirin with or without an HCV protease inhibitor (boceprevir, simeprevir or telaprevir).

   1.2 Genotype 2 or 3 infection
   Authorization of up to 12 weeks total may be granted for members without cirrhosis or with compensated cirrhosis who are treatment-naïve or failed prior treatment with PEG-IFN and ribavirin.

   1.3 Genotype 4, 5 or 6 infection
   Authorization of up to 12 weeks total may be granted for members without cirrhosis or with compensated cirrhosis who are treatment-naïve or who failed prior treatment with PEG-IFN and ribavirin with or without an HCV protease inhibitor (boceprevir, simeprevir or telaprevir).

   1.4 Decompensated cirrhosis (Child Turcotte Pugh [CTP] class B or C)
   Authorization of up to 24 weeks total may be granted for members with genotype 1 or 4 infection and decompensated cirrhosis and documented anemia (baseline hemoglobin [Hgb] below 10 g/dL) or RBV ineligibility (see Section III).

2. Chronic hepatitis C virus infection, in combination with ribavirin
   1.1 Genotype 2 infection
   Authorization of up to 12 weeks total may be granted for members without cirrhosis or with compensated cirrhosis who failed prior treatment with sofosbuvir and ribavirin.
1.2 Genotype 3 infection
   a. Authorization of up to 12 weeks total may be granted for members with the Y93H variant associated with velpatasvir resistance who are either of the following:
      i. Treatment-naïve with compensated cirrhosis
      ii. Failed prior treatment with PEG-IFN and ribavirin without cirrhosis
   b. Authorization of up to 12 weeks total may be granted for members with compensated cirrhosis who failed prior treatment with PEG-IFN and ribavirin.
   c. Authorization of up to 12 weeks total may be granted for members without cirrhosis or with compensated cirrhosis who failed prior treatment with sofosbuvir and ribavirin.

1.3 Decompensated cirrhosis (CTP class B or C)
   a. Authorization of up to 12 weeks total may be granted for members with genotype 1, 2, 3, 4, 5 or 6 infection and decompensated cirrhosis.
   b. Authorization of up to 24 weeks total may be granted for members with genotype 1 or 4 infection and decompensated cirrhosis who failed prior treatment with a sofosbuvir- or NSSA inhibitor-based regimen.

3. HCV and HIV coinfection
   Authorization may be granted for members with HCV and HIV coinfection who meet the following criteria:
   a. Member meets the criteria for approval for the requested regimen in Section II above.
   b. Member will not receive treatment with efavirenz, etravirine or nevirapine
   c. Member will not receive treatment with tipranavir

III. APPENDIX

RIBAVIRIN INELIGIBILITY
RBV ineligibility is defined as one or more of the below:
A. Intolerance to RBV
B. Pregnant female or male whose female partner is pregnant
C. Hemoglobinopathy
D. Coadministration with didanosine
OLYSIO (simeprevir)

I. INDICATIONS

FDA-Approved Indications
Olysio is a hepatitis C virus (HCV) NS3/4A protease inhibitor indicated for the treatment of chronic hepatitis C genotype 1 or 4 infection as a component of a combination antiviral treatment regimen.

II. EXCLUSIONS

A. Decompensated cirrhosis/moderate or severe hepatic impairment (Child Turcotte Pugh Class B or C)
B. Prior treatment failure with an HCV protease inhibitor (eg, telaprevir, boceprevir, simeprevir, paritaprevir) despite adequate dosing and duration of therapy

Note: When the requested drug is being used in a combination therapy regimen, exclusions to the other antiviral drugs also apply.

III. INITIAL CRITERIA FOR APPROVAL

1. Chronic hepatitis C virus infection, in combination with PEG-IFN and RBV
   1.1 Genotype 1 or 4 infection
   Authorization of up to 6 weeks total may be granted for initiation of therapy in members who are treatment-naïve or failed prior treatment with PEG-IFN and RBV AND meet one of the following criteria:
   A. Genotype 1a infection without the NS3 Q80K polymorphism
   B. Genotype 1b infection
   C. Genotype 4 infection

2. Chronic hepatitis C virus infection, in combination with Sovaldi
   2.1 Genotype 1a infection
   A. Authorization of up to 12 weeks total may be granted for members without cirrhosis who are treatment-naïve or failed prior treatment with PEG-IFN and RBV.
   B. Authorization of up to 24 weeks total may be granted for members with cirrhosis without the NS3 Q80K polymorphism who are treatment-naïve or failed prior treatment with PEG-IFN and RBV.
   2.2 Genotype 1b infection
   A. Authorization of up to 12 weeks total may be granted for members without cirrhosis who are treatment-naïve or failed prior treatment with PEG-IFN and RBV.
   B. Authorization of up to 24 weeks total may be granted for members with cirrhosis who are treatment-naïve or failed prior treatment with PEG-IFN and RBV.
2.3 Recurrent HCV infection post liver transplantation
Authorization of up to 12 weeks total may be granted for members with or without cirrhosis who have recurrent HCV genotype 1 infection post liver transplantation.

3. Chronic hepatitis C virus infection, in combination with Sovaldi and RBV
3.1 Genotype 1a infection
Authorization of up to 24 weeks total may be granted for members with cirrhosis without the NS3 Q80K polymorphism who are treatment-naïve or failed prior treatment with PEG-IFN and RBV.

3.2 Genotype 1b infection
Authorization of up to 24 weeks total may be granted for members with cirrhosis who are treatment-naïve or who have failed prior treatment with PEG-IFN and RBV.

3.3 Genotype 1 infection and previous failure of HCV NS5A inhibitor therapy
Authorization of up to 24 weeks total may be granted for members with cirrhosis who failed prior treatment with an HCV NS5A inhibitor and have NS5A inhibitor RAVs but do not have NS3 protease inhibitor RAVs.

3.4 Recurrent HCV infection post liver transplantation
See Section 2.3.

4. HCV and HIV Coinfection
Authorization may be granted for members who meet all of the following criteria:
A. Member meets the criteria for approval for the requested regimen above.
B. Member will not receive treatment with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitors.

IV. CONTINUATION OF THERAPY
Chronic hepatitis C virus infection, in combination with PEG-IFN and RBV
Genotype 1 or 4 infection
A. Week 4 assessment
B. Authorization of up to 12 weeks total may be granted for members with HCV-RNA < 25 IU/mL at week 4 of treatment.
IX. 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.

X. References