Description
Sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) is a fixed-dose combination oral tablet. Sofosbuvir is a nucleotide analog hepatitis C virus (HCV) NS5B polymerase inhibitor, velpatasvir is an NS5A inhibitor, and voxilaprevir is an NS3/4A protease inhibitor.

FDA Approved Indication(s)
Vosevi is indicated for the treatment of adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have:
- Genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor*;
- Genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor**.
  - Additional benefit of Vosevi over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.

* In clinical trials, prior NS5A inhibitor experience included daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir.
** In clinical trials, prior treatment experience included sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir).

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Vosevi is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Chronic Hepatitis C Infection (must meet all):
      1. Diagnosis of chronic HCV infection as evidenced by detectable serum HCV RNA levels by quantitative assay in the last 6 months;
      2. Member meets one of the following (a or b):
         a. HCV genotype is 1, 2, 3, 4, 5 or 6, and member has previously been treated with an HCV regimen containing one of the following NS5A inhibitors: daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir;
         b. HCV genotype is 1a or 3, and member has previously been treated with an HCV regimen containing sofosbuvir with or without any of the following: peginterferon
Clinical Policy
Sofosbuvir/Velpatasvir/Voxilaprevir

alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir);
*Chart note documentation and copies of lab results are required

3. Member must use Mavyret™ if member meets one of the following (a or b), unless contraindicated or clinically significant adverse effects are experienced (see Appendix E):
   a. HCV genotype 1 and member has previously been treated with an HCV regimen containing an NS5A inhibitor without an NS3/4A protease inhibitor (i.e., Daklinza®, Epclusa®, Harvoni®);
   b. HCV genotype is 1a or 3 and member has previously been treated with an HCV regimen containing sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir);

4. Prescribed by or in consultation with a gastroenterologist, hepatologist, infectious disease specialist, or provider who has expertise in treating HCV based on a certified training program (see Appendix F);

5. Age ≥ 18 years;

6. If cirrhosis is present, confirmation of Child-Pugh A status;

7. Member has received ≥ 8 weeks of the prior direct-acting antiviral agent (DAA) regimen from 2a or 2b above, unless virologic failure was determined prior to 8 weeks of therapy;

8. Life expectancy ≥ 12 months with HCV treatment;

9. Member agrees to participate in a medication adherence program meeting both of the following components (a and b):
   a. Medication adherence monitored by pharmacy claims data or member report;
   b. Member’s risk for non-adherence identified by adherence program or member/prescribing physician follow-up at least every 4 weeks;

10. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (see Section V Dosage and Administration for reference);

11. Dose does not exceed Vosevi (sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir) 100 mg (1 tablet) per day.

Approval duration: 12 weeks*
(*Approved duration should be consistent with a regimen in Section V Dosage and Administration)

B. Other diagnoses/indications
   1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and HIM.PHAR.21 for health insurance marketplace.

II. Continued Therapy
   A. Chronic Hepatitis C Infection (must meet all):
      1. Member meets one of the following (a or b):
         a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
         b. Must meet both of the following (i and ii):
i. Documentation supports that member is currently receiving Vosevi for chronic HCV infection and has recently completed at least 60 days of treatment with Vosevi;

ii. Member meets one of the following (1 or 2):
   1) HCV genotype is 1, 2, 3, 4, 5 or 6, and member has previously been treated with an HCV regimen containing one of the following NS5A inhibitors: daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir;
   2) If HCV genotype is 1a or 3, member has previously been treated with an HCV regimen containing sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir);

2. Member is responding positively to therapy;
3. Dose does not exceed Vosevi (sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir) 100 mg (1 tablet) per day.

**Approval duration: Up to a total treatment duration of 12 weeks**
(*Approved duration should be consistent with a regimen in Section V Dosage and Administration)

B. Other diagnoses/indications (must meet 1 or 2):
   1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and HIM.PHAR.21 for health insurance marketplace.

III. Diagnoses/Indications for which coverage is NOT authorized:
   A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – CP.CPA.09 for commercial and HIM.PHAR.21 for health insurance marketplace or evidence of coverage documents.

IV. Appendices/General Information
   **Appendix A: Abbreviation/Acronym Key**
   AASLD: American Association for the Study of Liver Diseases
   FDA: Food and Drug Administration
   HBV: hepatitis B virus
   HCV: hepatitis C virus
   HIV: human immunodeficiency virus
   IDSA: Infectious Diseases Society of America
   NS3/4A, NS5A/B: nonstructural protein
   PegIFN: pegylated interferon
   RBV: ribavirin
   RNA: ribonucleic acid

   **Appendix B: Therapeutic Alternatives**
   This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mavyret™</td>
<td>Treatment-experienced with IFN/pegIFN + RBV +/- sofosbuvir CHC infection:</td>
<td>Mavyret:</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Dose Limit/ Maximum Dose</td>
</tr>
<tr>
<td>-----------</td>
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<td>-------------------------</td>
</tr>
<tr>
<td>(glecaprevir /pibrentasvir)</td>
<td><strong>Genotypes 1, 2, 4, 5, or 6</strong>&lt;br&gt;Without cirrhosis:&lt;br&gt;Three tablets PO QD for 8 weeks&lt;br&gt;With compensated cirrhosis:&lt;br&gt;Three tablets PO QD for 12 weeks</td>
<td>glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day</td>
</tr>
<tr>
<td>Mavyret™ (glecaprevir /pibrentasvir)</td>
<td>Treatment-experienced with IFN/pegIFN + RBV +/- sofosbuvir CHC infection:&lt;br&gt;<strong>Genotype 3</strong>&lt;br&gt;Without cirrhosis or with compensated cirrhosis:&lt;br&gt;Three tablets PO QD for 16 weeks</td>
<td>Mavyret: glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day</td>
</tr>
<tr>
<td>Mavyret™ (glecaprevir /pibrentasvir)</td>
<td>Treatment-experienced with NS5A inhibitor without prior NS3/4A protease inhibitor CHC infection:&lt;br&gt;<strong>Genotype 1</strong>&lt;br&gt;Without cirrhosis or with compensated cirrhosis:&lt;br&gt;Three tablets PO QD for 16 weeks</td>
<td>Mavyret: glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day</td>
</tr>
<tr>
<td>Mavyret™ (glecaprevir /pibrentasvir)</td>
<td>Treatment-experienced with NS3/4A protease inhibitor without prior NS5A inhibitor CHC infection:&lt;br&gt;<strong>Genotype 1</strong>&lt;br&gt;Without cirrhosis or with compensated cirrhosis:&lt;br&gt;Three tablets PO QD for 12 weeks</td>
<td>Mavyret: glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day</td>
</tr>
<tr>
<td>Epclusa® (sofosbuvir/ velpatasvir)</td>
<td>With decompensated cirrhosis in whom prior sofosbuvir- or NS5A-based treatment experienced failed:&lt;br&gt;<strong>Genotype 1-6:</strong>&lt;br&gt;One tablet PO QD with weight-based RBV for 24 weeks</td>
<td>One tablet (sofosbuvir 400mg /velpatasvir 100 mg) per day</td>
</tr>
<tr>
<td>Epclusa® (sofosbuvir/ velpatasvir)</td>
<td>With compensated cirrhosis or without cirrhosis and non-NS5A inhibitor, sofosbuvir-containing regimen-experienced:&lt;br&gt;<strong>Genotype 1b:</strong>&lt;br&gt;One tablet PO QD for 12 weeks</td>
<td>One tablet (sofosbuvir 400mg /velpatasvir 100 mg) per day</td>
</tr>
</tbody>
</table>
Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s): coadministration with rifampin
- Boxed warning(s): risk of hepatitis B virus reactivation in patients coinfected with HCV and HBV

Appendix D: Direct-Acting Antivirals for Treatment of HCV Infection

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug Class</th>
<th>NS5A Inhibitor</th>
<th>Nucleotide Analog NS5B Polymerase Inhibitor</th>
<th>Non-Nucleoside NS5B Palm Polymerase Inhibitor</th>
<th>NS3/4A Protease Inhibitor (PI)</th>
<th>CYP3A Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daklinza</td>
<td>Daclatasvir</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Epclusa*</td>
<td>Velpatasvir</td>
<td>Sofosbuvir</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harvoni*</td>
<td>Ledipasvir</td>
<td>Sofosbuvir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mavyret*</td>
<td>Pibrentasvir</td>
<td>Gilecaprevir</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Olysio</td>
<td></td>
<td>Simeprevir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sovaldi</td>
<td></td>
<td>Sofosbuvir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technivie*</td>
<td>Ombitasvir</td>
<td>Paritaprevir</td>
<td>Ritonavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viekira XR/PAK*</td>
<td>Ombitasvir</td>
<td>Dasabuvir</td>
<td>Paritaprevir</td>
<td>Ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vosevi*</td>
<td>Velpatasvir</td>
<td>Sofosbuvir</td>
<td>Voxilaprevir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zepatier*</td>
<td>Elbasvir</td>
<td>Grazoprevir</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Combination drugs

Appendix E: General Information
- Hepatitis B Virus Reactivation (HBV) is a Black Box Warning for all direct-acting antiviral drugs for the treatment of HCV. HBV reactivation has been reported when treating HCV for patients co-infected with HBV, leading to fulminant hepatitis, hepatic failure, and death, in some cases. Patients should be monitored for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up, with treatment of HBV infection as clinically indicated.
- Acceptable medical justification for inability to use Mavyret (preferred product):
  - Severe hepatic disease (Child-Pugh C): use of Mavyret is not recommended due to higher exposures of glecaprevir and pibrentasvir.
  - Moderate hepatic disease (Child-Pugh B): although not an absolute contraindication, use of Mavyret is not recommended in patients with moderate hepatic disease (Child-Pugh B) due to lack of safety and efficacy data.
    - Following administration of Mavyret in HCV infected subjects with compensated cirrhosis (Child-Pugh A), exposure of glecaprevir was approximately 2-fold and pibrentasvir exposure was similar to non-cirrhotic HCV infected subjects.
    - At the clinical dose, compared to non-HCV infected subjects with normal hepatic function, glecaprevir AUC was 100% higher in Child-Pugh B subjects, and
increased to 11-fold in Child-Pugh C subjects. Pibrentasvir AUC was 26% higher in Child-Pugh B subjects, and 114% higher in Child-Pugh C subjects.

- Drug-drug interactions with one or more the following agents:
  - Atazanavir
  -Efavirenz

- Unacceptable medical justification for inability to use Mavyret (preferred product):
  - Black Box Warning (BBW): currently or previously infected with hepatitis B virus. This BBW is not unique to Mavyret, and it applies across the entire therapeutic class of direct-acting antivirals for treatment of HCV infection. Therefore it is not a valid clinical reason not to use Mavyret.
  - Concurrent anticoagulant therapy: Fluctuations in International Normalized Ratio (INR) have been observed in warfarin recipients who were also receiving treatment for HCV infections. This BBW is not unique to Mavyret, and it applies across the entire therapeutic class of direct-acting antivirals for treatment of HCV infection. Although caution is advised when using Mavyret while receiving concurrent anticoagulant therapy, specifically warfarin, this is not an absolute contraindication as long as patient is adequately monitored and educated during therapy.
  - Drug-drug interactions with one or more of the following agents:
    - Rifampin, carbamazepine, or St. John’s wort:
    - These drug-drug interactions are not unique to Mavyret, and they apply across the entire therapeutic class of direct-acting antivirals for treatment of HCV infection.

- Child-Pugh Score:

<table>
<thead>
<tr>
<th></th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bilirubin</strong></td>
<td>Less than 2 mg/dL</td>
<td>2-3 mg/dL</td>
<td>Over 3 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Less than 34 umol/L</td>
<td>34-50 umol/L</td>
<td>Over 50 umol/L</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>Over 3.5 g/dL</td>
<td>2.8-3.5 g/dL</td>
<td>Less than 2.8 g/dL</td>
</tr>
<tr>
<td></td>
<td>Over 35 g/L</td>
<td>28-35 g/L</td>
<td>Less than 28 g/L</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td>Less than 1.7</td>
<td>1.7 - 2.2</td>
<td>Over 2.2</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td>None</td>
<td>Mild / medically controlled</td>
<td>Moderate-severe / poorly controlled</td>
</tr>
<tr>
<td><strong>Encephalopathy</strong></td>
<td>None</td>
<td>Mild / medically controlled</td>
<td>Moderate-severe / poorly controlled. Grade III-IV</td>
</tr>
<tr>
<td><strong>Grade I-II</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grade III-IV</strong></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Child-Pugh class is determined by the total number of points: A = 5-6 points; B = 7-9 points; C = 10-15 points.

**Appendix F: Healthcare Provider HCV Training**

Acceptable HCV training programs and/or online courses include, but are not limited to the following:

- Hepatitis C online course ([https://www.hepatitisc.uw.edu/](https://www.hepatitisc.uw.edu/)): University of Washington is funded by the Division of Viral Hepatitis to develop a comprehensive, online self-study course for medical providers on diagnosis, monitoring, and management of hepatitis C virus infection. Free CME and CNE credit available.
- Fundamentals of Liver Disease ([https://liverlearning.aasld.org/fundamentals-of-liver-disease](https://liverlearning.aasld.org/fundamentals-of-liver-disease)): The AASLD, in collaboration with ECHO, the American College of Physicians
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(ACP), CDC, and the Department of Veterans Affairs, has developed Fundamentals of Liver Disease, a free, online CME course to improve providers’ knowledge and clinical skills in hepatology.

- Clinical Care Options: http://www.clinicaloptions.com/hepatitis.aspx
- CDC training resources: https://www.cdc.gov/hepatitis/resources/professionals/trainingresources.htm

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1-6: Treatment-experienced with NS5A inhibitor* with or without compensated cirrhosis</td>
<td>One tablet PO QD for 12 weeks</td>
<td>One tablet (sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg) per day</td>
<td>1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)</td>
</tr>
<tr>
<td>Genotype 1a or 3: Treatment-experienced with a sofosbuvir-containing regimen without NS5A inhibitor* with or without compensated cirrhosis</td>
<td>One tablet PO QD for 12 weeks</td>
<td></td>
<td>1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)</td>
</tr>
<tr>
<td>Genotype 3*: Treatment-naïve with compensated cirrhosis or pegIFN/RBV-experienced without cirrhosis with Y93H presence</td>
<td>One tablet PO QD for 12 weeks</td>
<td></td>
<td>AASLD-IDSA (updated May 2018)</td>
</tr>
<tr>
<td>Genotype 3*: Treatment-experienced with pegIFN/RBV with compensated cirrhosis</td>
<td>One tablet PO QD for 12 weeks</td>
<td></td>
<td>AASLD-IDSA (updated May 2018)</td>
</tr>
</tbody>
</table>

AASLD/IDSA treatment guidelines for chronic hepatitis C infection are updated at irregular intervals; refer to the most updated AASLD/IDSA guideline for most accurate treatment regimen.

* Off-label, AASLD-IDSA guideline-supported dosing regimen

VI. Product Availability
Tablet: sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg

VII. References

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created; per SDC and prior clinical guidance added HIM line of business to existing Commercial policy (modified policy number to CP.PCH.22, retire CP.CPA.290); added requirement that life expectancy ≥ 12 months with HCV treatment and participation in a medication adherence program.</td>
<td>12.03.19</td>
<td>02.20</td>
</tr>
<tr>
<td>Added new prescriber requirement to include a “provider who has expertise in treating HCV based on a certified training program”; added Appendix F (Healthcare Provider HCV Training).</td>
<td>11.18.19</td>
<td>02.20</td>
</tr>
<tr>
<td>Corrected reference from Appendix F to Appendix E in section I for requirement requiring redirection to Mavyret; added relevant information to Appendix E related to medical justification for inability to use Mavyret.</td>
<td>04.09.20</td>
<td></td>
</tr>
</tbody>
</table>

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and
limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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