Clinical Policy: Sofosbuvir/Velpatasvir (Epclusa)
Reference Number: CP.PHAR.268
Effective Date: 07.16
Last Review Date: 08.19
Line of Business: Medicaid

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Sofosbuvir/velpatasvir (Epclusa®) is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor.

FDA Approved Indication(s)
Epclusa is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection:
- Without cirrhosis or with compensated cirrhosis
- With decompensated cirrhosis for use in combination with ribavirin (RBV)

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 Epclusa 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. Confirmed HCV genotype is 1, 2, 3, 4, 5 or 6;
         *Chart note documentation and copies of lab results are required
      3. Documentation of the treatment status of the member (treatment-naive or treatment-experienced);
      4. Documentation of cirrhosis status of the member (no cirrhosis, compensated cirrhosis, or decompensated cirrhosis);
      5. Prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious disease specialist;
      6. Age ≥ 18 years;
      7. Member has at least one of the following contraindications to Mavyret™ (a or b):
         a. Decompensated cirrhosis (Child-Pugh B or C) confirmed by lab findings and clinical notes;
         b. Receiving treatment with efavirenz or atazanavir;
         *See Appendix E for additional details on acceptable contraindications
      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. 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 sofosbuvir/velpatasvir 400 mg/100 mg (1 tablet) per day.

Approval duration: up to a total of 24 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.PMN.53 for Medicaid.

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. Documentation supports that member is currently receiving Epclusa for chronic
         HCV infection and has recently completed at least 60 days of treatment with
         Epclusa;
   2. Member is responding positively to therapy;
   3. Dose does not exceed sofosbuvir/velpatasvir 400 mg/100 mg (1 tablet) per day.

Approval duration: up to a total of 24 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.PMN.53 for Medicaid.

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 policies –
   CP.PMN.53 for Medicaid 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
HCC: hepatocellular carcinoma
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>
</table>
| **Mavyret™ (glecaprevir/pibrentasvir)** | Treatment-naïve chronic HCV infection: **Genotypes 1, 2, 3, 4, 5, or 6**  
Without cirrhosis: Three tablets PO QD for 8 weeks  
With compensated cirrhosis: Three tablets PO QD for 12 weeks | Mavyret: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) per day |
| **Mavyret™ (glecaprevir/pibrentasvir)** | Treatment-experienced with IFN/pegIFN + RBV +/- sofosbuvir chronic HCV infection: **Genotypes 1, 2, 4, 5, or 6**  
Without cirrhosis: Three tablets PO QD for 8 weeks  
With compensated cirrhosis: Three tablets PO QD for 12 weeks | Mavyret: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) per day |
| **Mavyret™ (glecaprevir/pibrentasvir)** | Treatment-experienced with IFN/pegIFN + RBV +/- sofosbuvir chronic HCV infection: **Genotype 3**  
Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks | Mavyret: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) per day |
| **Mavyret™ (glecaprevir/pibrentasvir)** | Treatment-experienced with NS5A inhibitor without prior NS3/4A protease inhibitor chronic HCV infection: **Genotype 1**  
Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks | Mavyret: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) per day |
| **Mavyret™ (glecaprevir/pibrentasvir)** | Treatment-experienced with NS3/4A protease inhibitor without prior NS5A inhibitor chronic HCV infection: **Genotype 1**  
Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 12 weeks | Mavyret: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) per day |

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): Epclusa and RBV combination regimen is contraindicated in patients for whom RBV is contraindicated in patients for whom RBV is contraindicated. Refer to the RBV prescribing information for a list of contraindications for RBV.
- 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 Palmitate Polymerase Inhibitor</th>
<th>NS3/4A Protease Inhibitor (PI)</th>
<th>CYP3A Inhibitor</th>
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<tbody>
<tr>
<td>Daklinza</td>
<td>Daclatasvir</td>
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<tr>
<td>Epclusa*</td>
<td>Velpatasvir</td>
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<td></td>
<td>Sofosbuvir</td>
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<tr>
<td>Harvoni*</td>
<td>Ledipasvir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Mavyret*</td>
<td>Pibrentasvir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Glecaprevir</td>
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<tr>
<td>Olysio</td>
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<td></td>
<td></td>
<td></td>
<td>Simeprevir</td>
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<tr>
<td>Sovaldi</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Sofosbuvir</td>
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<tr>
<td>Technivie*</td>
<td>Omitasvir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Paritaprevir</td>
</tr>
<tr>
<td>Viekira XR/PAK*</td>
<td>Omitasvir</td>
<td></td>
<td>Dasabuvir</td>
<td></td>
<td></td>
<td>Paritaprevir</td>
</tr>
<tr>
<td>Vosevi*</td>
<td>Velpatasvir</td>
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<td></td>
<td></td>
<td></td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Zepatier*</td>
<td>Elbasvir</td>
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<td>Grazoprevir</td>
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</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.

### V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Genotype 1-6: Without cirrhosis or with compensated cirrhosis, treatment-naïve or RBV-experienced patient | One tablet PO QD for 12 weeks  
(GT 3 with compensated cirrhosis for pegIFN/RBV-experienced patient may use: one tablet PO QD with weight-based RBV for 12 weeks) † | One tablet (sofosbuvir 400 mg /velpatasvir 100 mg) per day | 1) FDA-approved labeling  
2) AASLD-IDSA (updated May 2018) |
| Genotype 1-6: With decompensated cirrhosis treatment-naïve or treatment-experienced* patient | One tablet PO QD with weight-based RBV for 12 weeks  
(GT 1, 4, 5, or 6 with decompensated cirrhosis and RBV-ineligible may use: one tablet PO QD for 24 weeks) ‡ | One tablet (sofosbuvir 400mg /velpatasvir 100 mg) per day | 1) FDA-approved labeling  
2) AASLD-IDSA (updated May 2018) |
## Indication

<table>
<thead>
<tr>
<th>Genotype 1-6: With decompensated cirrhosis in whom prior sofosbuvir- or NS5A-based treatment experienced failed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Regimen</td>
</tr>
<tr>
<td>One tablet PO QD with weight-based RBV for 24 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 1b: With compensated cirrhosis or without cirrhosis and non-NS5A inhibitor, sofosbuvir-containing regimen-experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Regimen</td>
</tr>
<tr>
<td>One tablet PO QD for 12 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 2: With or without compensated cirrhosis, sofosbuvir + RBV-experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Regimen</td>
</tr>
<tr>
<td>One tablet PO QD for 12 weeks</td>
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</table>

<table>
<thead>
<tr>
<th>Genotype 2 or 3: Treatment-naïve and treatment-experienced patients, post-liver transplant with compensated cirrhosis or decompensated cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Regimen</td>
</tr>
<tr>
<td>One tablet PO QD with weight-based RBV for 12 weeks</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 3 with NS5A Y93H polymorphism: Treatment-naïve with cirrhosis or treatment-experienced* patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Regimen</td>
</tr>
<tr>
<td>One tablet PO QD with weight-based RBV for 12 weeks</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.

*Treatment-experienced refers to previous treatment with NS3 protease inhibitor (telaprevir, boceprevir, or simeprevir) and/or peginterferon/RBV unless otherwise stated.

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

### VI. Product Availability

Tablet: sofosbuvir 400 mg with velpatasvir 100 mg
VII. References

Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Description</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>New policy created, split from CP.PHAR.17 Hepatitis C Therapies policy.</td>
<td>07.16</td>
<td>07.16</td>
</tr>
<tr>
<td>HCV RNA levels over six-month period added to confirm infection is chronic.</td>
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<tr>
<td>Life expectancy “≥12 months if HCC and awaiting transplant” is modified to indicate “≥12 months with HCV therapy.”</td>
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<tr>
<td>Methods to diagnose fibrosis/cirrhosis are modified to require a liver biopsy or a combination of one serologic and one radiologic test.</td>
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<tr>
<td>Serologic and radiologic tests are updated and correlated with METAVIR per Appendix C. Dosing regimens are presented in Appendix. Criteria is added requiring a verification of HCV RNA status at 4 weeks (and again at 6 weeks if present at 4) accordingly, the initial approval period is shortened to 8 weeks.</td>
<td></td>
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</tr>
<tr>
<td>Edited policy so congruent with the other HCV policies as follows: Testing criteria reorganized by cirrhosis status consistent with the regimen tables; HCC population broadened to incorporate those amenable to curative measures (resection, ablation, transplant). Fibrosure test that meets F3 requirement changed to ≥ 0.59. Criteria added excluding post-liver transplantation unless regimens specifically designate. Preferencing language edited for clarity. Removed creatinine clearance restriction. Under continuing approval, presence of HCV RNA is edited to remove specific timing of testing. Appendix B edited for clarity; Appendix C added. Appendix D – genotype “1” is footnoted to clarify possible subtypes. “Includes HCC” is removed from the decompensated cirrhosis. “Daily” is removed from the “recommended regimen” column; presentation of other data is abbreviated/short-handed.</td>
<td>08.16</td>
<td>09.16</td>
</tr>
<tr>
<td>Policy converted to new template. Added requirement for prevention of HBV reactivation. Consolidated appendix D and E into dosing and</td>
<td>08.17</td>
<td>09.17</td>
</tr>
</tbody>
</table>
administration in section V, added maximum dose requirement, initial approval duration expanded to full 12 weeks, limited continued therapy approval duration to 12 weeks, deleted viral load and adherence requirement in continued therapy, added documentation of positive response to therapy and continuity of care, and removed CIs in section II, added reference column in section V. Added preferencing information requiring Mavyret for FDA-approved indications. Safety criteria was applied according to the safety guidance discussed at CPAC and endorsed by Centene Medical Affairs. Exception made to require Hep B screening for all patients prior to treatment to ensure that proper risk reduction measures are taken.

3Q 2018 annual review: removed requirement for HBV verification; added requirement for documentation of treatment and cirrhosis status; expanded duration of tx required for COC from 30 days to 60 days; references reviewed and updated.

Removed advanced liver disease requirement to align with 2018 AASLD/IDSA hepatitis C treatment guidelines.

3Q 2019 annual review: removed documented sobriety from alcohol and illicit IV drugs for ≥ 6 months prior to starting therapy; references reviewed and updated.

**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.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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