Clinical Policy: Sofosbuvir/Velpatasvir (Epclusa)

Reference Number: GA.PMN.06
Effective Date: 12/16
Last Review Date: 2/19
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
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
   ** Provider must submit documentation (including office chart notes and lab results) supporting that member has met all approval criteria **

   A. Chronic Hepatitis C Infection (must meet all):
      1. Diagnosis of chronic hepatitis C virus (HCV) infection as evidenced by detectable HCV ribonucleic acid (RNA) levels over a six-month period;
      2. Age ≥ 18 years;
      3. Confirmed HCV genotype is 1, 2, 3, 4, 5 or 6;
         *Chart note documentation and copies of labs results are required
      4. Documentation of the treatment status of the patient (treatment-naïve or treatment-experienced);
      5. Documentation of cirrhosis status of the patient (no cirrhosis, compensated cirrhosis, or decompensated cirrhosis);
      6. Failure of Mavyret®/™, unless contraindicated or clinically significant adverse effects are experienced.
      7. At the time of request, member has none 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. Coadministration with efavirenz or atazanavir;
*See Appendix F for additional details on acceptable contraindications*

8. Life expectancy ≥ 12 months with HCV treatment;
9. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (see Appendix D and E for reference);
10. Member is hepatitis B virus (HBV) negative, or if positive, documentation that concurrent HBV infection is being treated (e.g., tenofovir alafenamide, adefovir, entecavir), unless contraindicated or clinically significant adverse effects are experienced (see Appendix F);
11. If prescribed with ribavirin, member has none of the following contraindications:
   a. Pregnancy or possibility of pregnancy - member or partner;
   b. Hypersensitivity to ribavirin;
   c. Coadministration with didanosine;
   d. Significant/unstable cardiac disease;
   e. Hemoglobinopathy (e.g., thalassemia major, sickle cell anemia);
   f. Hemoglobin < 8.5 g/dL.

**Approval duration: up to a total of 24 weeks**

(*Approved duration should be consistent with a regimen in Appendix D or E*)

**B. Other diagnoses/indications:** Refer to CP.PMN.53 – No Coverage Criteria/Off-Label Use Policy if diagnosis is NOT specifically listed under section I.

**II. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

<table>
<thead>
<tr>
<th>Definition</th>
<th>Abbreviation/Acronym</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASLD: American Association for the Study of Liver Diseases</td>
<td>AASLD</td>
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<tr>
<td>APRI: AST to platelet ratio</td>
<td>APRI</td>
</tr>
<tr>
<td>CTP: Child Turcotte Pugh</td>
<td>CTP</td>
</tr>
<tr>
<td>CrCl: creatinine clearance</td>
<td>CrCl</td>
</tr>
<tr>
<td>FDA: Food and Drug Administration</td>
<td>FDA</td>
</tr>
<tr>
<td>FIB-4: Fibrosis-4 index</td>
<td>FIB-4</td>
</tr>
<tr>
<td>HCC: hepatocellular carcinoma</td>
<td>HCC</td>
</tr>
<tr>
<td>HCV: hepatitis C virus</td>
<td>HCV</td>
</tr>
<tr>
<td>IDSA: Infectious Diseases Society of America</td>
<td>IDSA</td>
</tr>
<tr>
<td>MRE: magnetic resonance elastography</td>
<td>MRE</td>
</tr>
<tr>
<td>NS3/4A, NS5A/B: nonstructural protein</td>
<td>NS3/4A, NS5A/B</td>
</tr>
<tr>
<td>Peg-IFN: pegylated interferon</td>
<td>Peg-IFN</td>
</tr>
<tr>
<td>PI: protease inhibitor</td>
<td>PI</td>
</tr>
<tr>
<td>RBV: ribavirin</td>
<td>RBV</td>
</tr>
<tr>
<td>RNA: ribonucleic acid</td>
<td>RNA</td>
</tr>
</tbody>
</table>

*Appendix E:Abbreviation/Acronym Key*
### 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 300mg/pibrentasvir 120mg (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 300mg/pibrentasvir 120mg (3 tablets) per day |
| Mavyret™ (glecaprevir/pibrentasvir) | Treatment-experienced with IFN/pegIFN+RBV+-/ sofosbuvir chronic HCV infection: **Genotypes 3**  
Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks | Mavyret: glecaprevir 300mg/pibrentasvir 120mg (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 300mg/pibrentasvir 120mg (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 300mg/pibrentasvir 120mg (3 tablets) per day |
**Drug Name** | **Dosing Regimen** | **Dose Limit/Maximum Dose**
--- | --- | ---
Mavyret™ (glecaprevir/pibrentasvir) | Mavyret: glecaprevir 300mg/pibrentasvir 120mg (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**
- Epclusa and RBV combination regimen is contraindicated in patients for whom RBV is contraindicated. Refer to the RBV prescribing information for a list of contraindications for RBV.

**Appendix D: Approximate Scoring Equivalencies using META VIR F3/F4 as Reference**

<table>
<thead>
<tr>
<th>Fibrosis/ Cirrhosis</th>
<th>Serologic Tests*</th>
<th>Radiologic Tests†</th>
<th>Liver Biopsy‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FibroTest</td>
<td>FIBRO Spect II</td>
<td>APRI</td>
</tr>
<tr>
<td>Advanced fibrosis</td>
<td>≥0.59</td>
<td>≥42</td>
<td>&gt;1.5</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>≥0.75</td>
<td>≥42</td>
<td>&gt;1.5</td>
</tr>
</tbody>
</table>

*Serologic tests:
  - FibroTest (available through Quest as FibroTest or LabCorp as FibroSure)
  - FIBROSpect II (available through Prometheus Laboratory)
  - APRI (AST to platelet ratio index)
  - FIB-4 (Fibrosis-4 index: includes age, AST level, platelet count)

†Radiologic tests:
  - FibroScan (ultrasound-based elastography)
  - MRE (magnetic resonance elastography)

‡Liver biopsy (histologic scoring systems):
  - META VIR F3/F4 is equivalent to Knodell, Scheuer, and Batts-Ludwig F3/F4 and Ishak F4-5/F5-6
  - META VIR fibrosis stages: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = few septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis
Appendix E: Direct-Acting Antivirals for Treatment of HCV Infection

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NS5A Inhibitor</td>
</tr>
<tr>
<td>Daklinza</td>
<td>Daclatasvir</td>
</tr>
<tr>
<td>Epclusa*</td>
<td>Velpatasvir</td>
</tr>
<tr>
<td>Harvoni*</td>
<td>Ledipasvir</td>
</tr>
<tr>
<td>Olysio</td>
<td>Simeprevir</td>
</tr>
<tr>
<td>Sovaldi</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Technivie*</td>
<td>Ombitasvir</td>
</tr>
<tr>
<td>Viekira XR/PAK*</td>
<td>Ombitasvir</td>
</tr>
<tr>
<td>Zepatier*</td>
<td>Elbasvir</td>
</tr>
</tbody>
</table>

*Combination drugs

Appendix F: General Information

- Hepatitis B Virus (HBV) Reactivation 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 patient 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 approximatly 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 of 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 Ration (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.

- 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 the treatment of HCV infection.

### III. 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><strong>Genotype 1-6:</strong> Without cirrhosis or with compensated cirrhosis, treatment naïve or pegIFN/RBV-experienced patient</td>
<td>One tablet PO QD for 12 weeks</td>
<td>One tablet (sofosbuvir 400mg/velpatasvir 100mg) per day</td>
<td>1) FDA-approved labeling 2) AASLD-IDSA (updated September 2017)</td>
</tr>
<tr>
<td></td>
<td>(GT 3 with compensated cirrhosis for pegIFN/RBV-experienced patients may use: one tablet PO QD for 12 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Genotype 1-6:</strong> With decompensated cirrhosis treatment-naïve or treatment experienced* patient</td>
<td>One tablet PO QD for 12 weeks</td>
<td>One tablet (sofosbuvir 400mg/velpatasvir 100mg) per day</td>
<td>3) FDA-approved labeling 4) AASLD-IDSA (updated September 2017)</td>
</tr>
<tr>
<td></td>
<td>(GT 1, 4, 5, or 6 with decompensated cirrhosis and RBV-ineligible may use: one tablet PO QD for 24 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Genotype 1-6:</strong> With decompensated cirrhosis in whom prior sofosbuvir-or NS5A treatment experienced failed</td>
<td>One tablet PO QD with weight-based RBV for 24 weeks</td>
<td>One tablet (sofosbuvir 400mg/velpatasvir 100mg) per day</td>
<td>5) FDA-approved labeling 6) AASLD-IDSA (updated September 2017)</td>
</tr>
<tr>
<td><strong>Genotype 1b:</strong> With compensated cirrhosis or without cirrhosis and non-NS5A inhibitor, sofosbuvir-containing regimen-experienced</td>
<td>One tablet PO QD for 12 weeks</td>
<td>One tablet (sofosbuvir 400mg/velpatasvir 100mg) per day</td>
<td>7) FDA-approved labeling 8) AASLD-IDSA (updated September 2017)</td>
</tr>
<tr>
<td><strong>Genotype 2:</strong> With or without compensated cirrhosis,</td>
<td>One tablet PO QD for 12 weeks</td>
<td>One tablet (sofosbuvir)</td>
<td>9) FDA-approved labeling</td>
</tr>
<tr>
<td>Indication</td>
<td>Dosing Regimen</td>
<td>Maximum Dose</td>
<td>Reference</td>
</tr>
<tr>
<td>------------</td>
<td>----------------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>sofosbuvir +RBV-experienced</td>
<td>One tablet PO QD with weight-based RBV for 12 weeks</td>
<td>One tablet (sofosbuvir 400mg/velpatasvir 100mg) per day</td>
<td>10) AASLD-IDSA (updated September 2017)</td>
</tr>
<tr>
<td>Genotype 2 or 3: Treatment-naïve and treatment-experienced patients, post-liver transplant with compensated cirrhosis or decompensated cirrhosis</td>
<td>One tablet PO QD with weight-based RBV for 12 weeks</td>
<td>One tablet (sofosbuvir 400mg/velpatasvir 100mg) per day</td>
<td>11) FDA-approved labeling</td>
</tr>
<tr>
<td>Genotype 3 with NS5A Y93H polymorphism: Treatment-naïve with cirrhosis or treatment-experienced* patient</td>
<td>One tablet PO QD with weight-based RBV for 12 weeks</td>
<td>One tablet (sofosbuvir 400mg/velpatasvir 100mg) per day</td>
<td>13) FDA-approved labeling</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

**IV. Product Availability**

Tablet: sofosbuvir 400mg with velpatasvir 100mg

**V. References**


<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>Plan Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>New policy created, split from CP.PHAR.17 Hepatitis C Therapies policy. HCV RNA levels over six-month period added to confirm infection is chronic. Life expectancy “≥12 months if HCC and awaiting transplant” is modified to indicate “≥12 months with HCV therapy.” Methods to diagnose fibrosis/cirrhosis are modified to require a liver biopsy or a combination of one serologic and one radiologic test. 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>07/16</td>
<td>07/16</td>
</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>Removed criteria regarding medication prescribed by a specialist. Remove criteria regarding having HCC or advanced liver disease. Removed criteria regarding medication adherence program.</td>
<td>9/16</td>
<td>9/2016</td>
</tr>
</tbody>
</table>
Reviews, Revisions, and Approvals

| Removed criteria regarding sobriety from alcohol/illicit drugs |  |
| Added availability of full course of therapy as initial therapy consistent with appendix recommendation for initial criteria |  |
| Removed continuation criteria |  |
| Added preferencing information requiring Mavyret for FDA-approved indications. Added information requiring Hep B screening for all patients prior to treatment to ensure that proper risk reduction measures are taken. |  |
| Annual review. No changes made. |  |
| Changed current Georgia policy templates to corporate standard templates for drug coverage criteria to meet corporate compliance. Changes/revisions included; new formatting, font size, use of standard policy language for each section of policy, and rearranged order of certain steps in criteria and sections. Added new preferred treatment tables that includes dosage and frequency based on genotype for Mavyret. Removed background sections. Updated general information and contraindication section to be consistent with corporate HCV policies. |  |

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.

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This clinical policy does not constitute medical advice, medical treatment or medical care. It is
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professional medical judgment in providing the most appropriate care, and are solely responsible
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members and/or submitting claims for payment for such services.

**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
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