Clinical Policy: Glecaprevir/Pibrentasvir (Mavyret)
Reference Number: CP.CPA.285
Effective Date: 08.15.17
Last Review Date: 08.18
Line of Business: Commercial

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

Description
Glecaprevir and pibrentasvir (Mavyret™) are a fixed-dose combination of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor.

FDA Approved Indication(s)
Mavyret is indicated for the treatment of:
- Patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection*** without cirrhosis and with compensated cirrhosis (Child-Pugh A)
- Adult patients with genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor* or an NS3/4A protease inhibitor**, but not both

* In clinical trials, prior NS5A inhibitor experience included ledipasvir and sofosbuvir or Daclatasvir with pegylated interferon and ribavirin.
** In clinical trials, prior NS3/4A protease inhibitor experience included regimens containing Simeprevir and sofosbuvir, or Simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin.
*** In clinical trials, prior treatment experience included regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A protease inhibitor or NS5A inhibitor.

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 Mavyret 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 one of the following (a, b, or c);
         a. For treatment-naïve patients: genotypes 1, 2, 3, 4, 5, or 6;
         b. For patients treatment-experienced with interferon (IFN)/pegylated-interferon (pegIFN), ribavirin (RBV), and/or sofosbuvir only: genotypes 1, 2, 3, 4, 5, or 6;
         c. For patients treatment-experienced with either an NS5A inhibitor or an NS3/4A protease inhibitor: genotype 1 (see Appendix E);
      *Chart note documentation and copies of lab results are required
      3. Prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious disease specialist;
4. Age ≥ 18 years;
5. If cirrhosis is present, confirmation of Child-Pugh A status;
6. Member is not treatment-experienced with both NS3/4A protease inhibitor AND NS5A inhibitors, such as combination therapies including Technivie, Viekira, and Zepatier;
7. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (see Section V Dosage and Administration for reference);
8. Dose does not exceed glecaprevir 300 mg and pibrentasvir 120 mg (3 tablets) per day.

**Approval duration: up to a total of 16 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.

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 Mavyret for chronic HCV infection and has recently completed at least 40 days of treatment with Mavyret;
      ii. Confirmed HCV genotype is one of the following (1, 2, or 3):
         1) For treatment-naïve members: genotypes 1, 2, 3, 4, 5, or 6;
         2) For members treatment-experienced with interferon (IFN)/pegylated-interferon (pegIFN), ribavirin (RBV), and/or sofosbuvir only: genotypes 1, 2, 3, 4, 5, or 6;
         3) For members treatment-experienced with either an NS5A inhibitor or an NS3/4A protease inhibitor: genotype 1 (see Appendix E);

2. Member is responding positively to therapy;
3. Dose does not exceed glecaprevir 300 mg and pibrentasvir 120 mg (3 tablets) per day.

**Approval duration: up to a total of 16 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.

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 or evidence of coverage documents;
B. Treatment-experienced patients with both NS3/4A protease inhibitor AND NS5A inhibitor, such as combination therapies including: Technivie, Viekira, and Zepatier.

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
Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Patients with severe hepatic impairment (Child-Pugh C)
  - Co-administration with atazanavir or 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>
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</tr>
<tr>
<td>Epclusa*</td>
<td>Velpatasvir</td>
<td>Sofosbuvir</td>
<td></td>
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<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></td>
<td></td>
<td></td>
<td>Glecaprevir</td>
<td></td>
</tr>
<tr>
<td>Olysio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Simeprevir</td>
<td></td>
</tr>
<tr>
<td>Sovaldi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sofosbuvir</td>
<td></td>
</tr>
<tr>
<td>Technivie*</td>
<td>Ombitasvir</td>
<td></td>
<td></td>
<td></td>
<td>Paritaprevir</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Viekira XR/PAK*</td>
<td>Ombitasvir</td>
<td>Dasabuvir</td>
<td>Paritaprevir</td>
<td></td>
<td>Ritonavir</td>
<td></td>
</tr>
<tr>
<td>Vosevi*</td>
<td>Velpatasvir</td>
<td>Sofosbuvir</td>
<td></td>
<td></td>
<td>Voxilaprevir</td>
<td></td>
</tr>
<tr>
<td>Zepatier*</td>
<td>Elbasvir</td>
<td></td>
<td></td>
<td></td>
<td>Grazoprevir</td>
<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.

- Due to higher rates of virologic failure and treatment-emergent drug resistance, the data do not support labeling for treatment of HCV genotype 1 infected patients who are both NS3/4A PI and NS5A inhibitor-experienced.

- Child-Pugh Score:

<table>
<thead>
<tr>
<th>Child-Pugh Score</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 Grade I-II</td>
<td>Moderate-severe / poorly controlled. Grade III-IV</td>
</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

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>Genotypes 1-6: Treatment-naive</td>
<td>Without cirrhosis: Three tablets PO QD for 8 weeks</td>
<td>Three tablets (glecaprevir 300 mg/ pibrentasvir 120 mg) per day</td>
<td>1) FDA-approved labeling 2) AASLD-IDSA (updated September 2017)</td>
</tr>
<tr>
<td></td>
<td>With compensated cirrhosis: Three tablets PO QD for 12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotypes 1, 2, 4, 5, or 6: Treatment-experienced with IFN/pegIFN + RBV</td>
<td>Without cirrhosis: Three tablets PO QD for 8 weeks</td>
<td>Three tablets (glecaprevir 300 mg/ pibrentasvir 120 mg) per day</td>
<td>1) FDA-approved labeling 2) AASLD-IDSA (updated September 2017)</td>
</tr>
<tr>
<td></td>
<td>With compensated cirrhosis: Three tablets PO QD for 12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotypes 1 or 2: Treatment-experienced with sofosbuvir</td>
<td>Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 12 weeks</td>
<td>Three tablets (glecaprevir 300 mg/ pibrentasvir 120 mg) per day</td>
<td>1) FDA-approved labeling 2) AASLD-IDSA (updated September 2017)</td>
</tr>
<tr>
<td>Genotypes 3, 4, 5, or 6: Treatment-experienced with sofosbuvir</td>
<td>Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 12 weeks</td>
<td>Three tablets (glecaprevir 300 mg/ pibrentasvir 120 mg) per day</td>
<td>FDA-approved labeling</td>
</tr>
</tbody>
</table>
### Indication

| Genotype 3: Treatment-experienced with IFN/pegIFN + RBV |
| Genotype 1: Treatment-experienced with NS5A inhibitor* without prior NS3/4A protease inhibitor* |
| Genotype 1: Treatment-experienced with NS3/4A protease inhibitor* without prior NS5A inhibitor* |
| Genotype 1-6: Treatment-naïve or treatment-experienced, post-liver or kidney transplantation with or without compensated cirrhosis |

### Dosing Regimen

- Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks
- Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks
- Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 12 weeks
- Three tablets PO QD for 12 weeks (A 16-week treatment duration is recommended in genotype 1-infected patients who are NS5A inhibitor-experienced without prior treatment with an NS3/4A protease inhibitor or in genotype 3-infected patients who are PRS treatment-experienced)

### Maximum Dose

- Three tablets (glecaprevir 300 mg/pibrentasvir 120 mg) per day
- Three tablets (glecaprevir 300 mg/pibrentasvir 120 mg) per day
- Three tablets (glecaprevir 300 mg/pibrentasvir 120 mg) per day
- Three tablets (glecaprevir 300 mg/pibrentasvir 120 mg) per day

### Reference

1. FDA-approved labeling
2. AASLD-IDSA (updated September 2017)

### 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.

* See appendix E

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### VI. Product Availability

Tablets: glecaprevir 100 mg and pibrentasvir 40 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>Policy created. Safety criteria were 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 taking, though this is not specifically addressed in boxed warning.</td>
<td>08.15.17</td>
<td>08.17</td>
</tr>
<tr>
<td>Initial approval criteria was clarified from “up to a total of 16 weeks” to “8 to up to a total of 16 weeks” per Corporate P&amp;T feedback.</td>
<td>09.05.17</td>
<td>11.17</td>
</tr>
<tr>
<td>3Q 2018 annual review: removed requirement for HBV verification; added requirement that prescribed regimen should be consistent with FDA or AASLD recommendations; added specific examples of extrahepatic manifestations in appendix G; expanded duration of tx required for COC from 30 days 40 days; repeated in initial and continued approval criteria the requirement against treatment-experience with both NS3/4A protease inhibitor AND NS5A inhibitors, as previously only listed in section III. diagnoses/indications NOT allowed; references reviewed and updated.</td>
<td>05.22.18</td>
<td>08.18</td>
</tr>
<tr>
<td>Removed requirement for advanced fibrosis or other candidacy for therapy following approved clinical guidance; combined with and retired CP.CPA.EX.285 for HNAZ exchange lines of business.</td>
<td>09.03.18</td>
<td></td>
</tr>
<tr>
<td>No clinically significant changes: modifications made to update template.</td>
<td>01.07.19</td>
<td></td>
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</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.

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