Clinical Policy: Simeprevir (Olysio)
Reference Number: CP.PHAR.280
Effective Date: 09.16
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
Simeprevir (Olysio™) is an inhibitor of the hepatitis C virus (HCV) nonstructural protein 3/4A (NS3/4A) protease.

FDA Approved Indication(s)
Olysio is indicated for the treatment of adults with chronic HCV infection:
- In combination with sofosbuvir in patients with HCV genotype 1 without cirrhosis or with compensated cirrhosis
- In combination with peginterferon alfa (Peg-IFN-alfa) and ribavirin (RBV) in patients with HCV genotype 1 or 4 without cirrhosis or with compensated cirrhosis

Limitation(s) of use:
- Efficacy of Olysio in combination with Peg-IFN-alfa and RBV is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism.
- Olysio is not recommended in patients who have previously failed therapy with a treatment regimen that included Olysio or other HCV protease inhibitors.

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 Olysio 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 1;
         *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. 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;
6. Life expectancy ≥ 12 months with HCV treatment;
7. Member agrees to participate in a medication adherence program including 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;
8. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (see Section V Dosage and Administration for reference);
9. Dose does not exceed 150 mg (1 capsule) per day.

Approval duration: 12 weeks*
(*Approved duration should be consistent with a regimen in Section V Dosage and Administration; The AASLD/IDSA HCV guidance updated May 2018 no longer recommends use of simeprevir for the treatment of genotype 1 with compensated cirrhosis for 24 weeks)

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. Both of the following (i and ii):
         i. Documentation supports that member is currently receiving Olysio for chronic HCV infection and has recently completed at least 60 days of treatment with Olysio;
         ii. Confirmed HCV genotype 1;
   2. Member is responding positively to therapy;
   3. Dose does not exceed 150 mg (1 capsule) per day.

Approval duration: up to a total of 12 weeks*
(*Approved duration should be consistent with a regimen in Section V Dosage and Administration; The AASLD/IDSA HCV guidance updated May 2018 no longer recommends use of simeprevir for the treatment of genotype 1 with compensated cirrhosis for 24 weeks)

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
- 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™ (glecaprevir/pibrentasvir)</td>
<td>Treatment-naïve or treatment-experienced with PegIFN/RBV: <strong>Genotype 1</strong>&lt;br&gt;Without cirrhosis: Three tablets PO QD for 8 weeks&lt;br&gt;With compensated cirrhosis: Three tablets PO QD for 12 weeks</td>
<td>Mavyret: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) per day</td>
</tr>
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</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): Because Olysio is used only in combination with other antiviral drugs (including Peg-IFN-alfa and RBV) for the treatment of chronic HCV infection, the contraindications to other drugs also apply to the combination regimen.
- Boxed warning(s): risk of hepatitis B virus reactivation in patients coinfect 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>
</tr>
</thead>
<tbody>
<tr>
<td>Daklinza</td>
<td>Daclatasvir</td>
</tr>
<tr>
<td>Epclusa*</td>
<td>Velpatasvir Sofosbuvir</td>
</tr>
<tr>
<td>Harvoni*</td>
<td>Ledipasvir Sofosbuvir</td>
</tr>
<tr>
<td>Mavyret*</td>
<td>Pibrentasvir Glecaprevir</td>
</tr>
</tbody>
</table>
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>
<tbody>
<tr>
<td>Genotype 1: Treatment-naive or treatment-experienced patients without cirrhosis</td>
<td>Sovaldi 400 mg plus Olysio 150 mg PO QD for 12 weeks</td>
<td>Olysio: 150 mg/day</td>
<td>1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)</td>
</tr>
<tr>
<td>Genotype 1 or 4: Treatment-naïve and treatment-experienced liver transplant patients with or without compensated cirrhosis</td>
<td>Sovaldi 400 mg plus Olysio 150 mg PO QD with or without weight-based RBV for 12 weeks</td>
<td>Olysio: 150 mg/day</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.

Treatment-experienced refers to previous treatment with peginterferon/RBV unless otherwise stated.

The use of Olysio in combination with peginterferon and ribavirin for the treatment of chronic HCV GT 1 or 4 is no longer recommended by the AASLD/IDSA guidelines.

AASLD/IDSA HCV guidance updated May 2018 no longer recommends use of simeprevir for the treatment of genotype 1 with compensated cirrhosis or for the treatment of genotype 4.

VI. Product Availability

Capsule: 150 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>New policy created, split from CP.PHAR.17 Hepatitis C Therapies. 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.” Testing criteria reorganized by “no cirrhosis”/”cirrhosis” consistent with the regimen tables; HCC population is included under “cirrhosis” and broadened to incorporate HCC amenable to curative measures (resection, ablation, transplant). Methods to diagnose fibrosis/cirrhosis are modified to require presence of HCC, liver biopsy or a combination of one serologic and one radiologic test. Serologic and radiologic tests are updated and correlated with METAVIR per Appendix B. Removed creatinine clearance restriction. Criteria added excluding post-liver transplantation unless regimens specifically designate. Dosing regimens are presented in Appendix D and E per AASLD guidelines and FDA-approved indications. The initial approval is shortened to 8 weeks.</td>
<td>08.16</td>
<td>09.16</td>
</tr>
<tr>
<td>Policy converted to new template. Deleted references to peg-IFN as Olysio/RBV/peg-IFN is not recommended by AASLD; added requirement for prevention of HBV reactivation. Consolidated appendix D and E into dosing and administration in section V; added maximum dose requirement; initial approval duration expanded to full 24 weeks, limited continued therapy approval duration to 24 weeks, deleted viral load and adherence requirement in continued, 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.</td>
<td>08.17</td>
<td>09.17</td>
</tr>
<tr>
<td>Removed the following language: “If a lower cost alternative regimen carries an equal or higher AASLD-IDSA rating, a clinical contraindication or intolerance must be present for the alternative regimen prior to approval.”</td>
<td></td>
<td>09.17</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.

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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