Clinical Policy: Simeprevir (Olysio)
Reference Number: GA.PMN.18
Product: Medicaid
Effective Date: 12/16
Last Review Date: 3/18

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

Description
The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for simeprevir (Olysio®).

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

I. 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. Age ≥ 18 years;
   2. Diagnosis of chronic hepatitis C virus (HCV) infection as evidenced by detectable HCV ribonucleic acid (RNA) levels over a six-month period;
   3. Confirmed HCV genotype is 1;
   4. Life expectancy ≥ 12 months with HCV treatment;
   5. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (see Appendix D and E for reference);
   6. If member is without cirrhosis or with compensated cirrhosis (Child-Pugh A): Mayvret is preferred unless contraindication or intolerance
   7. 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 B);
   8. Creatinine clearance ≥ 50 mL/min if prescribed with peginterferon alfa-2b and ribavirin;
   9. Member has none of the following contraindications:
      a. If Olysio is prescribed with peginterferon or ribavirin:
         i. Hypersensitivity to peginterferon alfa or ribavirin, whichever is requested;
         ii. Pregnancy or possibility of pregnancy - member or partner;
         iii. Significant/unstable cardiac disease;
      b. If Olysio is prescribed with ribavirin:
         i. Co-administration with didanosine;
         ii. Hemoglobinopathy (e.g., thalassemia major, sickle cell anemia);
         iii. Hemoglobin < 8.5 g/dL.
      c. If Olysio is prescribed with peginterferon:
i. Autoimmune hepatitis;
ii. Decompensated hepatic disease (e.g., Child-Pugh class B or C).

**Approval duration: up to a total of 48 weeks***
(*Approved duration should be consistent with a regimen in Appendix D or E)

**B. Other diagnoses/indications:** Refer to CP.PHAR.57 - Global Biopharm Policy.

**Background**

*Description/Mechanism of Action:*

Olysio (simeprevir) is an inhibitor of the HCV NS3/4A protease and a direct-acting antiviral (DAA) agent against the hepatitis C virus.

**Olysio Formulations**

Capsule, Oral

- Olysio: 150 mg

**Ribavirin Formulations**

Capsule, Oral:

- Rebetol: 200 mg
- Ribosphere: 200 mg
- Generic: 200 mg

Solution, Oral:

- Rebetol: 40 mg/mL (100 mL)

Tablet, Oral:

- Copegus: 200 mg
- Moderiba (includes dose packs): 200 mg, 400 mg, 600 mg
- Ribosphere: 200 mg, 400 mg, 600 mg
- Ribosphere RibaPak (dose packs): 200 mg, 400 mg, 600 mg
- Generic: 200 mg

**Peginterferon Alfa-2a Formulations:**

Solution, Subcutaneous [preservative free]:

- Pegasys: 180 mcg/mL (1 mL); 180 mcg/0.5 mL (0.5 mL)
- Pegasys ProClick: 135 mcg/0.5 mL (0.5 mL)
- Pegasys ProClick: 180 mcg/0.5 mL (0.5 mL)

**Peginterferon Alfa-2b Formulations:**

Kit, Subcutaneous [preservative free]:

- Peg-Intron Redipen: 50 mcg/0.5 mL, 80 mcg/0.5 mL, 120 mcg/0.5 mL, 150 mcg/0.5 mL
- Peg-Intron Redipen Pak 4: 120 mcg/0.5 mL
- PegIntron: 50 mcg/0.5 mL, 80 mcg/0.5 mL, 120 mcg/0.5 mL, 150 mcg/0.5 mL
- Sylatron: 200 mcg, 300 mcg, 600 mcg

**FDA Approved Indications:**

Olysio is an HCV NS3/4A protease inhibitor/oral capsule formulation indicated for:
CLINICAL POLICY
Simeprevir

- 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.

Limitations 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 at baseline compared to patients infected with HCV genotype 1a without the 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.

Appendices
Appendix A: Abbreviation Key
HCV: hepatitis C virus
APRI: AST to platelet ratio
AASLD: American Association for the Study of Liver Diseases
CTP: Child Turcotte Pugh
CrCl: creatinine clearance
FIB-4: Fibrosis-4 index
HIV-1: human immunodeficiency virus
HCC: hepatocellular carcinoma
IDSA: Infectious Diseases Society of America
MRE: magnetic resonance elastography
PI: protease inhibitor
RBV: ribavirin
RNA: ribonucleic acid

Appendix B: Approximate Scoring Equivalencies using METAVIR 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>Fibro Test</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>

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):
METAVIR F3/F4 is equivalent to Knodell, Scheuer, and Batts-Ludwig F3/F4 and Ishak F4-5/F5-6
METAVIR fibrosis stages: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = few septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis

Appendix C: Direct-Acting Antivirals for Treatment of HCV Infection
## CLINICAL POLICY

### Simeprevir

<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>
<td></td>
<td></td>
</tr>
<tr>
<td>Epclusa*</td>
<td>Velpatasvir</td>
<td>Sofosbuvir</td>
<td></td>
<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>Olysio</td>
<td></td>
<td></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></td>
<td></td>
<td></td>
<td></td>
<td>Paritaprevir</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>Zepatier*</td>
<td>Elbasvir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grazoprevir</td>
</tr>
</tbody>
</table>

*Combination drugs

**Additional PIs no longer recommended: Victrelis (boceprevir), Incivek (telaprevir)

### Appendix D: FDA-Approved Regimens and Treatment Durations

<table>
<thead>
<tr>
<th>Treatment Naive/Experienced</th>
<th>Genotype</th>
<th>Failed Treatment Regimen</th>
<th>Recommended Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Cirrhosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment naive</td>
<td>1*</td>
<td>None</td>
<td>Sovaldi + Olysio§</td>
</tr>
<tr>
<td></td>
<td>1*, 4</td>
<td>None</td>
<td>Olysio + Peg-IFN-alfá + RBV (12 weeks) then Peg-IFN-alfá + RBV (12 weeks)† <strong>If genotype 1a, negative for the Q80K variant. Also labeled for HCV/HIV-1 coinfection.</strong></td>
</tr>
<tr>
<td>Treatment experienced</td>
<td>1*</td>
<td>Peg-IFN-based therapy</td>
<td>Sovaldi + Olysio§</td>
</tr>
<tr>
<td></td>
<td>1*, 4</td>
<td>Peg-IFN-based therapy</td>
<td>Olysio + Peg-IFN-alfá + RBV (12 weeks) then Peg-IFN-alfá + RBV (12 weeks)† <strong>If genotype 1a, negative for Q80K variant. Also labeled for HCV/HIV-1 coinfection.</strong></td>
</tr>
</tbody>
</table>

Compensated Cirrhosis (CTP/Child-Pugh Class A)

| Treatment naive             | 1*       | None                     | Sovaldi + Olysio†   |
|                             | 1*, 4     | None                     | Olysio + Peg-IFN-alfá + RBV (12 weeks) then Peg-IFN-alfá + RBV (12 weeks)† **If genotype 1a, negative for the Q80K variant.** |
|                             |          |                          | Olysio + Peg-IFN-alfá + RBV (12 weeks) then Peg-IFN-alfá + RBV (36 weeks)‡ **If genotype 1a, negative for Q80K variant. Limited to HCV/HIV-1 coinfection.** |
## CLINICAL POLICY

### Simeprevir

<table>
<thead>
<tr>
<th>Treatment Naive/ Experienced</th>
<th>Genotype</th>
<th>Failed Treatment Regimen</th>
<th>Recommended Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment experienced</td>
<td>1*</td>
<td>Peg-IFN-based therapy</td>
<td>Sovaldi + Olysio†</td>
</tr>
</tbody>
</table>
|                              | 1*, 4    | Peg-IFN-based therapy     | Olysio + Peg-IFN-alfa + RBV (12 weeks) then Peg-IFN-alfa + RBV (36 weeks)‡  
  If genotype 1a, negative for the Q80K variant. Also labeled for HCV/HIV-1 coinfection. |

*Subtype a or b, or unknown subtype  
§Treatment duration - 12 weeks  
†Treatment duration - 24 weeks  
‡Treatment duration – 48 weeks

### Appendix E: AASLD-IDSA Recommended Regimens and Treatment Durations

<table>
<thead>
<tr>
<th>Treatment Naive/ Experienced</th>
<th>Genotype</th>
<th>Failed Treatment Regimen</th>
<th>Recommended Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis</td>
<td>1a, 1b</td>
<td>None</td>
<td>Sovaldi + Olysio§</td>
</tr>
<tr>
<td>Treatment experienced</td>
<td>1a, 1b</td>
<td>Peg-IFN/RBV</td>
<td>Sovaldi + Olysio§</td>
</tr>
</tbody>
</table>
| Not specified                | 1*, 4    | Not specified             | Sovaldi + Olysio +/- RBV§  
  If post-liver transplantation. |

<table>
<thead>
<tr>
<th>Compensated Cirrhosis (CTP/Child-Pugh Class A)</th>
<th>Genotype</th>
<th>Failed Treatment Regimen</th>
<th>Recommended Regimen</th>
</tr>
</thead>
</table>
| Treatment naive                                 | 1a       | None                      | Sovaldi + Olysio +/- RBV†  
  If negative for the Q80K variant. |
|                                                | 1b       | None                      | Sovaldi + Olysio†       |
| Treatment experienced                          | 1a       | Peg-IFN/RBV               | Sovaldi + Olysio +/- RBV†  
  If negative for the Q80K variant. |
|                                                | 1b       | Peg-IFN/RBV               | Sovaldi + Olysio +/- RBV†       |
| Not specified                                  | 1*, 4    | Not specified             | Sovaldi + Olysio +/- RBV§  
  If post-liver transplantation. |

*Subtype a or b, or unknown subtype  
§Treatment duration - 12 weeks  
†Treatment duration - 24 weeks

### Appendix F: General Information

- Hepatitis B Reactivation is a black box warning for all direct-acting antiviral drugs for the treatment of HCV. The provider must provide either:
  - Documentation of absence of concurrent HBV infection as evidenced by laboratory values showing absence of hepatitis B virus envelope antigen (HBeAg) and HBV DNA;
  - Documentation that HBV co-infected patient may not be candidates for therapy as evidenced by one of the following:
CLINICAL POLICY
Simeprevir

- Absence of HBeAg, HBV DNA less than 2,000 international units/mL, and alanine aminotransferase (ALT) level within 1 to 2 times the upper limit of normal;
- HBeAg-positive and HBV DNA greater than 1,000,000 international units/mL and ALT level within 1 to 2 times the upper limit of normal;
  - Documentation that concurrent HBV infection is being treated (e.g., tenofovir alafenamide, adefovir, entecavir), unless contraindicated or clinically significant adverse effects are experienced

- The 2016 AASLD/IDSA treatment guideline for HBV consider ALT levels <30 U/L for men and <19 U/L for women as upper limits of normal.
- The 2016 AASLD/IDSA treatment guideline for HBV recommend adults with compensated cirrhosis, even with low levels of viremia (<2,000 IU/mL) be treated with antiviral therapy to reduce the risk of decompensation, regardless of ALT level. The recommendation extends to adults with decompensated cirrhosis be treated with antiviral therapy indefinitely regardless of HBV DNA level, HBeAg status, or ALT level to decrease the risk of worsening liver-related complications.
- The 2017 AASLD/IDSA treatment guideline for HCV no longer recommend use of simeprevir in treatment of chronic HCV genotype 4.

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>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>Removed criteria regarding medication prescribed by a specialist Remove criteria regarding having HCC or advanced liver disease Removed criteria regarding medication adherence program Removed criteria regarding sobriety from alcohol/illicit drugs</td>
<td>10/16</td>
<td>10/2016</td>
</tr>
<tr>
<td>Added availability of full course of therapy as initial therapy consistent with appendix recommendation for initial criteria Removed continuation criteria</td>
<td>4/17</td>
<td></td>
</tr>
<tr>
<td>Added preferencing information requiring Mavyret for FDA-approved indications. Exception made to require Hep B screening. Removed</td>
<td>9/17</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Policy
Simeprevir

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>indication for Genotype 4 as 2017 guidelines do not recommend use for genotype 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual review. No changes made.</td>
<td>3/18</td>
<td></td>
</tr>
</tbody>
</table>

References
14. PegIntron Prescribing Information. Whitehouse Station, NJ: Merck Sharp and Dohme Corp.; February 2016. Available at
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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound.
by such terms and conditions by providing services to 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 policy.

**Note:** For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at [http://www.cms.gov](http://www.cms.gov) for additional information.

©2016 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.