Clinical Policy: Elbasvir/Grazoprevir (Zepatier)
Reference Number: GA.PMN.16
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 elbasvir/grazoprevir (Zepatier™).

Policy/Criteria
It is the policy of health plans affiliated with Centene Corporation® that Zepatier 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 RNA (ribonucleic acid) levels over a six-month period;
   3. Confirmed HCV genotype is 1 or 4;
   4. For genotype 1a, laboratory testing for the presence or absence of virus with NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93;
   5. If member is without cirrhosis or with compensated cirrhosis (Child-Pugh A); Mavyret is preferred unless contraindication or intolerance
   6. Life expectancy ≥ 12 months with HCV treatment;
   7. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (see Appendix D and E for reference);
   8. 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);
   9. Member has none of the following contraindications:
      a. Moderate to severe hepatic impairment (Child-Pugh B and C);
      b. Co-administration with efavirenz or organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors or strong inducers of CYP 450 (CYP3A) including: phenytoin, carbamazepine, rifampin, St. John’s Wort, atazanavir, darunavir, lopinavir, saquinavir, tipranavir, cyclosporine;
      c. If prescribed with ribavirin, member has none of the following contraindications:
         i. Pregnancy or possibility of pregnancy - member or partner;
         ii. Hypersensitivity to ribavirin;
         iii. Coadministration with didanosine;
iv. Significant/unstable cardiac disease;
v. Hemoglobinopathy (e.g., thalassemia major, sickle cell anemia);
vi. Hemoglobin < 8.5 g/dL.

**Approval duration: up to a total of 16 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:*
Zepatier is a fixed-dose combination tablet containing elbasvir and grazoprevir for oral administration. Elbasvir is an HCV NS5A inhibitor, and grazoprevir is an HCV NS3/4A protease inhibitor. Each tablet contains 50 mg elbasvir and 100 mg grazoprevir.

**Zepatier Formulations**
- Tablet, Oral:
  - Zepatier: 50 mg elbasvir and 100 mg grazoprevir

**Ribavirin Formulations**
- Capsule, Oral:
  - Rebetol: 200 mg
  - Ribasphere: 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
  - Ribasphere: 200 mg, 400 mg, 600 mg
  - Ribasphere RibaPak (dose packs): 200 mg, 400 mg, 600 mg
  - Generic: 200 mg

**FDA Approved Indications:**
Zepatier is a fixed-dose combination oral tablet formulation / NS5A inhibitor/NS3/4A protease inhibitor indicated with or without ribavirin for:
- Treatment of chronic HCV genotypes 1 or 4 infection in adults.

**Appendices**

**Appendix A: Abbreviation Key**
- APRI: AST to platelet ratio
- AASLD: American Association for the Study of Liver Diseases
- CTP: Child Turcotte Pugh
- CTP: Child Turcotte Pugh
- DAA: direct acting antiviral
- FIB-4: Fibrosis-4 index
- HCC: hepatocellular carcinoma
- HCV: hepatitis C virus
- IDSA: Infectious Diseases Society of America
- MRE: magnetic resonance elastography

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**Clinical Policy**

**Elbasvir/Grazoprevir**

NS3/4A, NS5A/B: nonstructural protein  
Peg-IFN: pegylated interferon  
RBV: ribavirin

**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>

*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):
- 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 (DAAs) 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>
<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>
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<tr>
<td>Technivie*</td>
<td>Ombitasvir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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></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>
<th>See footnotes for duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis or Compensated Cirrhosis (CTP/Child-Pugh Class A)</td>
<td>1a</td>
<td>None</td>
<td>Zepatier §&lt;br&gt;If no baseline NS5A polymorphisms.&lt;br&gt;Zepatier + RBV ○&lt;br&gt;If baseline NS5A polymorphisms.</td>
<td></td>
</tr>
<tr>
<td>Treatment naive</td>
<td>1b, 4</td>
<td>None</td>
<td>Zepatier §</td>
<td></td>
</tr>
<tr>
<td>Treatment experienced</td>
<td>1a</td>
<td>Peg-IFN/RBV</td>
<td>Zepatier §&lt;br&gt;If no baseline NS5A polymorphisms.&lt;br&gt;Zepatier + RBV ○&lt;br&gt;If baseline NS5A polymorphisms.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1a, 1b</td>
<td>NS3/Peg-IFN/RBV **</td>
<td>Zepatier + RBV §</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>Peg-IFN/RBV</td>
<td>Zepatier §</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Peg-IFN/RBV</td>
<td>Zepatier + RBV ○</td>
<td></td>
</tr>
</tbody>
</table>

**NS3 includes Victrelis (boceprevir), Incivek (telaprevir) or Olysio (simeprevir)

§Treatment duration - 12 weeks
○Treatment duration – 16 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>
<th>See footnotes for duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis or Compensated Cirrhosis (CTP/Child-Pugh Class A)</td>
<td>1a</td>
<td>None</td>
<td>Zepatier §&lt;br&gt;If no baseline NS5A polymorphisms.&lt;br&gt;Zepatier ○&lt;br&gt;If baseline NS5A polymorphisms.</td>
<td></td>
</tr>
<tr>
<td>Treatment naive</td>
<td>1b, 4</td>
<td>None</td>
<td>Zepatier §</td>
<td></td>
</tr>
<tr>
<td>Treatment experienced</td>
<td>1*</td>
<td>NS3 PI/Peg-IFN/RBV **</td>
<td>Zepatier + RBV ○&lt;br&gt;If baseline NS5A polymorphisms.&lt;br&gt;Zepatier + RBV §</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td>Peg-IFN/RBV</td>
<td>Zepatier + RBV ○&lt;br&gt;If baseline NS5A polymorphisms.&lt;br&gt;Zepatier + RBV §&lt;br&gt;If no baseline NS5A polymorphisms.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1b, 4</td>
<td>Peg-IFN/RBV</td>
<td>Zepatier + RBV §</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Peg-IFN/RBV</td>
<td>Zepatier + RBV ○</td>
<td></td>
</tr>
</tbody>
</table>

*Subtype a or b, or unknown subtype

**NS3 includes Victrelis (boceprevir), Incivek (telaprevir) or Olysio (simeprevir)

§Treatment duration - 12 weeks
○Treatment duration – 16 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:
    - 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 (ULN);
    - HBeAg-positive and HBV DNA greater than 1,000,000 international units/mL and ALT level within 1 to 2 times the ULN;
  - 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 ULN.

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.

<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</td>
<td>10/16</td>
<td>10/2016</td>
</tr>
<tr>
<td>Remove criteria regarding having HCC or advanced liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Removed criteria regarding medication adherence program</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Removed criteria regarding sobriety from alcohol/illicit drugs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Added availability of full course of therapy as initial therapy consistent with appendix recommendation for initial criteria.  Removed continuation criteria.

Added requirement of documentation of NS5A resistance-associated polymorphisms.  Added preferencing information requiring Mavyret for FDA-approved indications.  Added requirement for 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.

Annual review.  No changes made.

References

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 for additional information.