Clinical Policy: Elbasvir/Grazoprevir (Zepatier)
Reference Number: CP.PCH.16
Effective Date: 01.01.20
Last Review Date: 02.20
Line of Business: Commercial, HIM

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

Description
Grazoprevir/elbasvir (Zepatier®) is a fixed-dose combination product containing elbasvir, a hepatitis C virus (HCV) NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor.

FDA Approved Indication(s)
Zepatier is indicated for treatment of chronic HCV genotype 1 or 4 infection in adults. Zepatier is indicated for use with ribavirin in certain patient populations.

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 Zepatier 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 1 or 4;
         *Chart note documentation and copies of lab results are required
      3. 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;
      4. Documentation of the treatment status of the patient (treatment-naive or treatment-experienced);
      5. If cirrhosis is present, confirmation of Child-Pugh A status;
      6. Prescribed by or in consultation with a gastroenterologist, hepatologist, infectious disease specialist, or provider who has expertise in treating HCV based on a certified training program (see Appendix F);
      7. Age ≥ 18 years;
      8. Life expectancy ≥ 12 months with HCV treatment;
      9. Member agrees to participate in a medication adherence program meeting 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;
      10. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (see Section V Dosage and Administration for reference);
11. Dose does not exceed Zepatier (elbasvir/grazoprevir) 50 mg/100 mg (1 tablet) 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 and HIM.PHAR.21 for health insurance marketplace..

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 Zepatier for chronic HCV infection and has recently completed at least three quarters of the full regimen with Zepatier;
      ii. Confirmed HCV genotype is 1 or 4;
2. Member is responding positively to therapy;
3. Dose does not exceed Zepatier (elbasvir/grazoprevir) 50 mg/100 mg (1 tablet) 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 and HIM.PHAR.21 for health insurance marketplace..

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 and HIM.PHAR.21 for health insurance marketplace 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
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 moderate or severe hepatic impairment (Child-Pugh B or C) due to the expected significantly increased grazoprevir plasma concentration and the increased risk of alanine aminotransferase (ALT) elevations
  - With inhibitors of organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors that are known or expected to significantly increase grazoprevir plasma concentrations, strong CYP3A inducers, and efavirenz
  - If Zepatier is administered with RBV, the contraindications to RBV also apply.
- 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>
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<tbody>
<tr>
<td></td>
<td>NS5A Inhibitor</td>
</tr>
<tr>
<td>Daklinza</td>
<td>Daclatasvir</td>
</tr>
<tr>
<td>Epclusa*</td>
<td>Velpatasvir</td>
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<tr>
<td>Harvoni*</td>
<td>Ledipasvir</td>
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<tr>
<td>Mavyret*</td>
<td>Pibrentasvir</td>
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<tr>
<td>Olysio</td>
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<tr>
<td>Sovaldi</td>
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<tr>
<td>Technivie*</td>
<td>Ombitasvir</td>
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<tr>
<td>Viekira XR/PAK*</td>
<td>Ombitasvir</td>
</tr>
<tr>
<td>Vosevi*</td>
<td>Velpatasvir</td>
</tr>
<tr>
<td>Zepatier*</td>
<td>Elbasvir</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.
- For patients infected with HCV Genotype 1a: Testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended. Clinical trial results show decreased efficacy of Zepatier in HCV genotype 1a with presence of NS5A
polymorphisms. If baseline NS5A polymorphisms are present for genotype 1a, refer to Section VI on the longer recommended duration of therapy.

- According to the September 2017 AASLD/IDSA HCV guidance updates, Zepatier plus Sovaldi is a recommended treatment option for patients treatment-experienced with pegIFN/RBV with compensated cirrhosis and genotype 3.

- Child-Pugh Score:

<table>
<thead>
<tr>
<th></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</td>
<td>Grade I-II</td>
</tr>
<tr>
<td></td>
<td>Mild / medically controlled</td>
<td>Grade III-IV</td>
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Child-Pugh class is determined by the total number of points: A = 5-6 points; B = 7-9 points; C = 10-15 points.

Appendix F: Healthcare Provider HCV Training
Acceptable HCV training programs and/or online courses include, but are not limited to the following:

- Hepatitis C online course ([https://www.hepatitisc.uw.edu/](https://www.hepatitisc.uw.edu/)): University of Washington is funded by the Division of Viral Hepatitis to develop a comprehensive, online self-study course for medical providers on diagnosis, monitoring, and management of hepatitis C virus infection. Free CME and CNE credit available.

- Fundamentals of Liver Disease ([https://liverlearning.aasld.org/fundamentals-of-liver-disease](https://liverlearning.aasld.org/fundamentals-of-liver-disease)): The AASLD, in collaboration with ECHO, the American College of Physicians (ACP), CDC, and the Department of Veterans Affairs, has developed Fundamentals of Liver Disease, a free, online CME course to improve providers’ knowledge and clinical skills in hepatology.


- CDC training resources: [https://www.cdc.gov/hepatitis/resources/professionals/trainingresources.htm](https://www.cdc.gov/hepatitis/resources/professionals/trainingresources.htm)

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Genotype 1a: Treatment-naïve or pegIFN/RBV-experienced with or without compensated cirrhosis without baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93</td>
<td>One tablet PO QD for 12 weeks</td>
<td>One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day</td>
<td>1) FDA-approved labeling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2) AASLD-IDSA (updated May 2018)</td>
</tr>
<tr>
<td>Indication</td>
<td>Dosing Regimen</td>
<td>Maximum Dose</td>
<td>Reference</td>
</tr>
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<td>---------------------------------------------------------------------------</td>
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<td>------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Genotype 1a: Treatment-naïve or PegIFN/RBV experienced with or without compensated cirrhosis with baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93 | One tablet PO QD plus weight-based RBV for 16 weeks                            | One tablet (grazoprevir 100 mg/elbasvir 50 mg) per day        | 1) FDA-approved labeling  
AASLD-IDSA (updated May 2018)                                           |
| Genotype 1b: Treatment-naïve or PegIFN/RBV experienced with or without compensated cirrhosis | One tablet PO QD for 12 weeks                                                 | One tablet (grazoprevir 100 mg/elbasvir 50 mg) per day      | 1) FDA-approved labeling  
AASLD-IDSA (updated May 2018)                                           |
| Genotype 1a or 1b: pegIFN/RBV/NS3 PI* - experienced with or without compensated cirrhosis without baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93 | One tablet PO QD plus weight-based RBV for 12 weeks                            | One tablet (grazoprevir 100 mg/elbasvir 50 mg) per day      | 1) FDA-approved labeling  
AASLD-IDSA (updated May 2018)                                           |
| Genotype 1a or 1b: pegIFN/RBV/NS3 PI* - experienced with or without compensated cirrhosis with baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93 | One tablet PO QD plus weight-based RBV for 16 weeks                            | One tablet (grazoprevir 100 mg/elbasvir 50 mg) per day      | 1) FDA-approved labeling  
AASLD-IDSA (updated May 2018)                                           |
| Genotype 3*: pegIFN/RBV-experienced with compensated cirrhosis           | One tablet PO QD plus sofosbuvir 400 mg for 12 weeks                          | One tablet (grazoprevir 100 mg/elbasvir 50 mg) per day      | AASLD-IDSA (updated May 2018)                                           |
| Genotype 4: Treatment-naïve with or without compensated cirrhosis        | One tablet PO QD for 12 weeks                                                 | One tablet (grazoprevir 100 mg/elbasvir 50 mg) per day      | 1) FDA-approved labeling  
AASLD-IDSA (updated May 2018)                                           |
| Genotype 4: PegIFN/RBV-experienced with or without compensated cirrhosis with virologic relapse/failure | Virologic relapse after prior pegIFN/RBV therapy: One tablet PO QD for 12 weeks | One tablet (grazoprevir 100 mg/elbasvir 50 mg) per day      | AASLD-IDSA (updated May 2018)                                           |
Indication | Dosing Regimen | Maximum Dose | Reference
--- | --- | --- | ---
Virologic failure while on pegIFN/RBV therapy: One tablet PO QD plus weight-based RBV for 16 weeks

*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.*

* NS3 protease inhibitor = telaprevir, boceprevir, or simeprevir

ǂ Off-label, AASLD-IDSA guideline-supported dosing regimen

VI. Product Availability
Tablet: grazoprevir 100 mg with elbasvir 50 mg

VII. References

### Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
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<tr>
<td>12.03.19</td>
<td>02.20</td>
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Policy created; per SDC and prior clinical guidance added HIM line of business to existing Commercial policy (modified policy number to CP.PCH.16, retire CP.CPA.284); added requirement that life expectancy ≥ 12 months with HCV treatment and participation in a medication adherence program.

Added new prescriber requirement to include a “provider who has expertise in treating HCV based on a certified training program”; Appendix F (Healthcare Provider HCV Training) added.
**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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