Clinical Policy: Elbasvir/Grazoprevir (Zepatier)
Reference Number: CP.CPA.284
Effective Date: 11.01.16
Last Review Date: 08.19
Line of Business: Commercial

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 or infectious disease specialist;
      7. Age ≥ 18 years;
      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 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 CP.CPA.09 if diagnosis is NOT specifically listed under section III
   (Diagnoses/Indications for which coverage is NOT authorized).

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 CP.CPA.09 if diagnosis is NOT specifically listed under section III
   (Diagnoses/Indications for which coverage is NOT authorized).

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 or evidence of coverage documents.

IV. Appendices/General Information
Appendix A: Abbreviation/Acronym Key
AASLD: American Association for the
Study of Liver Diseases                                      IDSA: Infectious Diseases Society of
FDA: Food and Drug Administration                            America
HBV: hepatitis B virus                                         NS3/4A, NS5A/B: nonstructural protein
HCV: hepatitis C virus                                         PegIFN: pegylated interferon
HIV: human immunodeficiency virus                             RBV: ribavirin
RNA: ribonucleic acid

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
• Contraindication(s):
  o 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>
<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>
<td>Epclusa*</td>
<td>Velpatasvir</td>
<td>Sofosbuvir</td>
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<td>Harvoni*</td>
<td>Ledipasvir</td>
<td>Sofosbuvir</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>Technievie*</td>
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<tr>
<td>Viekira XR/PAK*</td>
<td>Ombitasvir</td>
<td></td>
<td>Dasabuvir</td>
<td>Paritaprevir</td>
<td>Ritonavir</td>
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</tr>
<tr>
<td>Vosevi*</td>
<td>Velpatasvir</td>
<td>Sofosbuvir</td>
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<tr>
<td>Zepatier*</td>
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</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>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>Less than 2 mg/dL</td>
<td>2-3 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Less than 34 umol/L</td>
<td>34-50 umol/L</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>
</table>
| 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 | One tablet PO QD for 12 weeks                       | One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day                  | 1) FDA-approved labeling  
2) AASLD-IDSA (updated May 2018) |
| 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  
2) 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  
2) 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  
2) AASLD-IDSA (updated May 2018) |
| Genotype 1a or 1b: pegIFN/RBV/NS3 PI* - experienced with or without | 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  
2) AASLD-IDSA (updated May 2018) |
<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>compensated cirrhosis with baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93</td>
<td>elbasvir 50 mg per day</td>
<td>2) AASLD-IDSA (updated May 2018)</td>
<td></td>
</tr>
<tr>
<td>Genotype 3(^\d): pegIFN/RBV-experienced with compensated cirrhosis</td>
<td>One tablet PO QD plus sofosbuvir 400 mg for 12 weeks</td>
<td>One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day</td>
<td>AASLD-IDSA (updated May 2018)</td>
</tr>
<tr>
<td>Genotype 4: Treatment-naive with or without compensated cirrhosis</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 2) AASLD-IDSA (updated May 2018)</td>
</tr>
<tr>
<td>Genotype 4: PegIFN/RBV-experienced with or without compensated cirrhosis with virologic relapse/failure</td>
<td>Virologic relapse after prior pegIFN/RBV therapy: One tablet PO QD for 12 weeks</td>
<td>One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day</td>
<td>AASLD-IDSA (updated May 2018)</td>
</tr>
<tr>
<td></td>
<td>Virologic failure while on pegIFN/RBV therapy: One tablet PO QD for 12 weeks</td>
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</tr>
<tr>
<td></td>
<td>Virologic relapse after prior pegIFN/RBV therapy: One tablet PO QD for 12 weeks</td>
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</tr>
<tr>
<td></td>
<td>One tablet PO QD plus weight-based RBV for 16 weeks</td>
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</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.

* NS3 protease inhibitor = telaprevir, boceprevir, or simeprevir

† 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>Description</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy converted to new template from “Zepatier NATL 11.16.16.docx”. Annual Review – added requirement for tx status, and cirrhosis status for consistency; added trial of Epclusa for those not a candidate for Harvoni; added re-direction to Epclusa if &gt;12 week request for Harvoni.</td>
<td>06.17</td>
<td>11.17</td>
</tr>
<tr>
<td>Added redirection to Mavyret for FDA-approved indications and as an option in addition to Epclusa for Harvoni requests &gt;12 weeks. 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>09.05.17</td>
<td>11.17</td>
</tr>
<tr>
<td>3Q 2018 annual review: removed requirement for HBV verification; added age limit; added requirement for documentation of Child-Pugh A status if cirrhosis is present; added requirement for documentation of treatment status; removed redirection to Epclusa or Mavyret if treatment duration is greater than 12 weeks since parity and rediretions no longer shorten duration of tx; added requirement that prescribed regimen should be consistent with FDA or AASLD recommendations; expanded duration of tx required for COC from 30 days to three quarters of the full regimen; required verification of genotype for COC; removed conditional requirement for RBV CI; 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.284 for HNAZ exchange lines of business.</td>
<td>09.03.18</td>
<td></td>
</tr>
<tr>
<td>No clinically significant changes: removed Harvoni, Epclusa, and Mavyret trial requirement in line with previously approved clinical guidance.</td>
<td>01.07.19</td>
<td></td>
</tr>
<tr>
<td>3Q 2019 annual review: no clinically significant changes; references reviewed and updated.</td>
<td>05.24.19</td>
<td>08.19</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.

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