INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document (Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document) may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

NPF Coverage Policy

Cigna covers grazoprevir/elbasvir (Zepatier®) as medically necessary when the following criteria are met for FDA Indications or Other Uses with Supportive Evidence:

Prior authorization is recommended for prescription benefit coverage of Zepatier. Criteria are based on the guidance issued by American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA), prescribing information, clinical data, and expert review. Approval durations differ by baseline characteristics. Because of the specialized skills required for evaluation and diagnosis of individuals treated with Zepatier as well as the monitoring required for adverse events (AEs) and efficacy, approval requires Zepatier to be prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician.

FDA Indication(s)

1. **Chronic Hepatitis C Virus (HCV) Genotype 1a.** Approve for the specified duration below if individuals meet the following criteria (A, B, and C):
   A) The individual is ≥ 18 years of age; AND
B) Zepatier is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND

C) The individual meets ONE of the following criteria (i or ii):
   i. Approve for 12 weeks if the individual meets ONE of the following conditions (a or b):
      a) Condition 1 (individuals must meet [1] or [2], PLUS [3]):
         (1) The individual is treatment-naïve; OR
         (2) The individual has previously been treated with pegylated interferon + ribavirin only; AND
         (3) The individual does NOT have a baseline NS5A polymorphism at ONE (or more) of the following the amino acid positions: 28, 30, 31, or 93; OR
      b) Condition 2 (individuals must meet [1] and [2]):
         (1) The individual has previously been treated with pegylated interferon + ribavirin and an HCV protease inhibitor; AND
         (2) Zepatier will be prescribed in combination with ribavirin.
   ii. Approve for 16 weeks if the individual meets the following criteria (a or b, PLUS c and d):
      a) The individual is treatment-naïve; OR
      b) The individual has previously been treated with pegylated interferon + ribavirin only; OR
      c) The individual has a baseline NS5A polymorphism at ONE (or more) of the following amino acid positions: 28, 30, 31, or 93; AND
      d) Zepatier will be prescribed in combination with ribavirin.

2. Chronic Hepatitis C Virus (HCV) Genotype 1b. Approve for 12 weeks if individuals meet the following criteria (A, B, and C):
   A) The individual is ≥ 18 years of age; AND
   B) Zepatier is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
   C) The individual meets ONE of the following conditions (i or ii):
      i. Condition 1 (individuals must meet a or b):
         a) The individual is treatment-naïve; OR
         b) The individual has previously been treated with pegylated interferon + ribavirin only; OR
      ii. Condition 2 (individuals must meet a and b):
         a) The individual has previously been treated with pegylated interferon + ribavirin + an HCV protease inhibitor; AND
         b) Zepatier will be prescribed in combination with ribavirin.

3. Chronic Hepatitis C Virus (HCV) Genotype 4. Approve for the duration specified below if individuals meet the following criteria (A, B, and C):
   A) The individual is ≥ 18 years of age; AND
   B) Zepatier is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
   C) The individual meets ONE of the following conditions (i or ii):
      i. Approve for 12 weeks if the individual is treatment-naïve; OR
      ii. Approve for 16 weeks if the individual has previously been treated with pegylated interferon and ribavirin for HCV and Zepatier will be prescribed in combination with ribavirin.

Other Uses with Supportive Evidence

4. Individual Has Been Started on Zepatier. Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Approve the duration described above to complete a course therapy (e.g., an individual who should receive 12 weeks, and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

Conditions Not Covered

Grazoprevir/elbasvir (Zepatier®) is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all inclusive):
1. Hepatitis C Virus (HCV), Child-Pugh Class B or Child-Pugh Class C Liver Disease (Moderate or Severe Hepatic Impairment). Zepatier is contraindicated in individuals with moderate or severe hepatic impairment (Child-Pugh Class B or C).¹

2. Hepatitis C Virus (HCV) [any genotype], Combination with Any Other Direct-Acting Antivirals (DAAs) [Not Including Ribavirin]. Zepatier provides a complete antiviral regimen for individuals with genotype 1 and 4 chronic HCV.

3. Life Expectancy Less Than 12 Months Due to Non-Liver Related Comorbidities. According to AASLD guidance, little evidence exists to support initiation of HCV treatment in individuals with limited life expectancy (less than 12 months) due to non–liver-related comorbid conditions.⁵ For these individuals, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence.

4. Pediatric Individuals (Age < 18 Years). The safety and efficacy of Zepatier have not been established in pediatric individuals < 18 years of age.¹ Guidelines recommend Harvoni (ledipasvir/sofosbuvir tablets) in pediatric individuals with genotypes 1 or 4 chronic HCV.⁵

5. Retreatment with Zepatier in Individuals Who Have Previously Received Zepatier (e.g., retreatment in prior null responders, prior partial responders, prior relapse individuals, individuals who have not completed a course of therapy due to an adverse reaction or for other reasons).

### Background

#### Overview
Zepatier is an oral fixed-dose combination tablet containing grazoprevir, a second generation protease inhibitor and elbasvir, an NS5A inhibitor, indicated with or without ribavirin for the treatment of genotypes 1 and 4 chronic hepatitis C virus (HCV) in adults.¹ Zepatier is contraindicated in individuals with Child-Pugh B or C liver disease (decompensated cirrhosis). Zepatier is also contraindicated with inhibitors of organic anion transporting polypeptides 1B1/3 (OATP1B1/3) that are known or expected to significantly increase grazoprevir plasma concentrations, strong inducers of cytochrome P450 (CYP)3A, and efavirenz.

#### Dosing
The recommended dosage of Zepatier is one co-formulated tablet containing 50 mg of grazoprevir and 100 mg of elbasvir once daily (QD) with or without food.¹ The duration of treatment is outlined below (Table 1) and is dependent on the individual population. Prior to initiating Zepatier in individuals with genotype 1a infection, testing for the NS5A resistance associated polymorphism is recommended to guide treatment duration. In individuals with genotype 1a and this polymorphism present at baseline, 12 weeks of treatment with Zepatier resulted in lower rates of sustained viral response 12 weeks after treatment completion (SVR12) relative to individuals with genotype 1a without the presence of this baseline polymorphism.

#### Table 1. Recommended Zepatier Dosage Regimens for the Treatment of Genotype 1 or 4 Chronic HCV.¹

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment History</th>
<th>Baseline NS5A Polymorphism</th>
<th>Treatment Regimen</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>TN/PR-experienced, without NS5A polymorphisms†</td>
<td>No†</td>
<td>Zepatier</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1a</td>
<td>TN/PR-experienced, with baseline NS5A polymorphisms‡</td>
<td>Yes‡</td>
<td>Zepatier + ribavirin‡</td>
<td>16 weeks</td>
</tr>
<tr>
<td>1a or 1b</td>
<td>PR + HCV PI-experienced§</td>
<td>NA</td>
<td>Zepatier + ribavirin‡</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1b</td>
<td>TN/TE*</td>
<td>NA</td>
<td>Zepatier</td>
<td>12 weeks</td>
</tr>
<tr>
<td>4</td>
<td>TN</td>
<td>NA</td>
<td>Zepatier</td>
<td>12 weeks</td>
</tr>
<tr>
<td>4</td>
<td>PR-experienced†</td>
<td>NA</td>
<td>Zepatier + ribavirin‡</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>
HCV – Hepatitis C virus; TN – Treatment naïve; PR- Pegylated interferon/ribavirin; † Individuals who have failed treatment with PR; ‡ NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93; § For individuals with creatinine clearance (CrCl) > 50 mL/min, the recommended dose of ribavirin is weight-based. For individuals with CrCl ≤ 50 mL/min, including individuals receiving hemodialysis, refer to the ribavirin prescribing information for the correct ribavirin dosage; The optimal Zepatier-based treatment regimen and duration of therapy for PR + HCV protease inhibitor (PI)-experienced genotype 1a-infected individuals with one or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, and 93 has not been established; PI – PI – Protease inhibitor; †† NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93; NA – Not applicable.

Guidelines
NS5A RAS testing is recommended for genotype 1a-infected, treatment-naive or -experienced individuals being considered for Zepatier. If present, a different regimen should be considered. Zepatier is recognized as a recommended treatment option in individuals with genotype 1 or 4 chronic HCV in guidelines.5

References

Last Revision Details

| Annual revision | No criteria changes | 03/25/2020 |

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