



## PRIOR AUTHORIZATION POLICY

**POLICY:** Hepatitis C – Zepatier® (grazoprevir/elbasvir tablets – Merck)

**TAC APPROVAL DATE:** 03/06/2019

### 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.<sup>1</sup> Zepatier is contraindicated in patients 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.<sup>1</sup> The duration of treatment is outlined below (Table 1) and is dependent on the patient population. Prior to initiating Zepatier in patients with genotype 1a infection, testing for the NS5A resistance associated polymorphism is recommended to guide treatment duration. In patients 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 patients 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.<sup>1</sup>**

Genotype	Treatment History	Baseline NS5A Polymorphism	Treatment Regimen	Treatment Duration
1a	TN/PR-experienced* without NS5A polymorphisms <sup>†</sup>	No <sup>†</sup>	Zepatier	12 weeks
1a	TN/PR-experienced* <u>with</u> baseline NS5A polymorphisms <sup>†</sup>	Yes <sup>†</sup>	Zepatier + ribavirin <sup>‡</sup>	16 weeks
1a <sup>§</sup> or 1b	PR + HCV PI-experienced <sup>β</sup>	NA	Zepatier + ribavirin <sup>‡</sup>	12 weeks
1b	TN/TE <sup>†</sup>	NA	Zepatier	12 weeks
4	TN	NA	Zepatier	12 weeks
4	PR-experienced*	NA	Zepatier + ribavirin <sup>‡</sup>	16 weeks

HCV – Hepatitis C virus; TN – Treatment naïve; PR– Pegylated interferon/ribavirin; \* Patients who have failed treatment with PR; <sup>†</sup> NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93; <sup>‡</sup> For patients with creatinine clearance (CrCl) > 50 mL/min, the recommended dose of ribavirin is weight-based. For patients with CrCl ≤ 50 mL/min, including patients receiving hemodialysis, refer to the ribavirin prescribing information for the correct ribavirin dosage; <sup>§</sup> The optimal Zepatier-based treatment regimen and duration of therapy for PR + HCV protease inhibitor (PI)-experienced genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, and 93 has not been established; PI – PI – Protease inhibitor; <sup>β</sup> Patients who have failed treatment with PR + and NS3/4A PI (i.e., Victrelis® [boceprevir capsules], Incivek® [telaprevir tablets], or Olysio® [simeprevir capsules]); NA – Not applicable.

### Guidelines

The American Association for the Study of Liver Diseases (AASLD) recommended regimens are detailed in the [Hepatitis C Virus Direct-Acting Antivirals Therapy Class Summary](#).<sup>5</sup> For the most up-to-date recommendations always consult the [guidelines](#). NS5A RAS testing is recommended for genotype 1a-infected, treatment-naïve or -experienced patients being considered for Zepatier. In general, if RASs are present, weight-based ribavirin (WBR) should be added and treatment extended to 16 weeks, or a

different recommended therapy used. Zepatier is recognized as a recommended or alternative treatment option in patients with genotype 1 or 4 chronic HCV in guidelines.<sup>5</sup>

### **POLICY STATEMENT**

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 patients 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.

**Automation:** None.

### **RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of Zepatier is recommended in those who meet the following criteria:

#### **FDA-Approved Indications**

- 1. Chronic Hepatitis C Virus (HCV) Genotype 1a.** Approve for the specified duration below if patients meet the following criteria (A, B, and C):
  - A) The patient is  $\geq 18$  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 patient meets ONE of the following criteria (i or ii):
    - i. Approve for 12 weeks if the patient meets ONE of the following conditions (a or b):
      - a) Condition 1 (patients must meet [1] or [2], PLUS [3]):
        - (1) The patient is treatment-naïve; OR
        - (2) The patient has previously been treated with pegylated interferon + ribavirin *only*; AND
        - (3) The patient 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 (patients must meet [1] and [2]):
        - (1) The patient 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 patient meets the following criteria (a or b, PLUS c and d):
      - a) The patient is treatment-naïve; OR
      - b) The patient has previously been treated with pegylated interferon + ribavirin *only*; AND
      - c) The patient 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 patients meet the following criteria (A, B, and C):
  - A) The patient is  $\geq 18$  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 patient meets ONE of the following conditions (i or ii):
    - i. Condition 1 (patients must meet a or b):
      - a) The patient is treatment-naïve; OR
      - b) The patient has previously been treated with pegylated interferon + ribavirin *only*; OR
    - ii. Condition 2 (patients must meet a and b):
      - a) The patient 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 patients meet the following criteria (A, B, and C):
- A) The patient is  $\geq 18$  years of age; AND
  - B) Zepatier is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician;
  - C) The patient meets ONE of the following conditions (i or ii):
    - i. Approve for 12 weeks if the patient is treatment-naïve; OR
    - ii. Approve for 16 weeks if the patient 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. **Patient 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., a patient who should receive 12 weeks, and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

#### CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zepatier has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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 patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).<sup>1</sup>
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 patients 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 patients with limited life expectancy (less than 12 months) due to non-liver-related comorbid conditions.<sup>5</sup> For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence.

4. **Pediatric Patients (Age < 18 Years).** The safety and efficacy of Zepatier have not been established in pediatric patients < 18 years of age.<sup>1</sup> Guidelines recommend Harvoni (ledipasvir/sofosbuvir tablets) in pediatric patients with genotypes 1 or 4 chronic HCV.<sup>5</sup>
5. **Retreatment with Zepatier in Patients Who Have Previously Received Zepatier** (e.g., retreatment in prior null responders, prior partial responders, prior relapse patients, patients who have not completed a course of therapy due to an adverse reaction or for other reasons).
6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## REFERENCES

1. Zepatier™ tablets [prescribing information]. Whitehouse Station, NJ: Merck; June 2018.
2. Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naïve and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. *Lancet*. 2015;386(10003):1537-1545.
3. Zeuzem S, Ghalib R, Reddy R, et al. Grazoprevir-elbasvir combination therapy for treatment-naïve cirrhotic and non-cirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection. *Ann Intern Med*. 2015;163:1-13.
4. Forns X, Gordon SC, Zuckerman E, et al. Grazoprevir and elbasvir plus ribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent. *J Hepatol*. 2015;63:564-572.
5. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Updated May 24, 2018. Available at: <http://www.hcvguidelines.org>. Accessed on February 5, 2019.
6. Forns X, Gordon SC, Zuckerman E, et al. Grazoprevir and elbasvir plus ribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent. *J Hepatol*. 2015;63:564-572.
7. Rockstroh JR, Nelson M, Katlama C, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (E-EDGE CO-INFECTION): a non-randomized, open-label trial. *Lancet HIV*. 2015;2(8):e319-327.
8. Brown A, Hezode C, Zuckerman E, et al. C-SCAPE: Efficacy and safety of 12 weeks of grazoprevir +/- elbasvir +/- ribavirin in patients with HCV GT2, 4, 5, or 6 infection P0771. *J Hepatology*. 2015; 62 (Suppl 2):S619.
9. Kwo P, Gane EJ, Peng CY, et al. Effectiveness of elbasvir and grazoprevir combination, with or without ribavirin, for treatment-experienced patients with chronic hepatitis C infection. *Gastroenterology*. 2017;152:164-175.

## HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New policy	New policy	02/03/2016
DEU revision	Updated guidelines	--
Selected revision	HCV, Child-Pugh B or C added to conditions not recommended for approval.	08/17/2016
Annual revision	No criteria changes	02/15/2017
Annual revision	No criteria changes	02/28/2018
Annual revision	No criteria changes	03/06/2019

TAC – Therapeutic Assessment Committee; \* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>.