Clinical Policy: Elbasvir/Grazoprevir (Zepatier)

Reference Number: ERX.SPA.132
Effective Date: 10.01.16
Last Review Date: 08.21
Line of Business: Commercial, Medicaid

Revision Log

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 the 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 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 member (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, or provider who has expertise in treating HCV based on a certified training program (*see Appendix F)*;
7. Age ≥ 18 years;
8. Member has contraindication(s) or clinically significant adverse effects to Harvoni® and Epclusa® (*see Appendix E*);
9. Life expectancy ≥ 12 months with HCV treatment;
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 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 ERX.PA.01 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 a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
   b. 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 60 days of treatment with Zepatier;
      ii. Confirmed HCV genotype is 1 or 4;
2. Member is responding positively to therapy;
3. Dose does not exceed 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 ERX.PA.01 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 – ERX.PA.01 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
HCC: hepatocellular carcinoma
HCV: hepatitis C 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

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Harvoni® (ledipasvir/ sofosbuvir)	**Genotype 1** Treatment-naïve without cirrhosis, who are HIV-uninfected, AND whose HCV viral load is less than 6 million IU/mL: One tablet PO QD for 8 weeks* Treatment-naïve without cirrhosis (not meeting the 8 week treatment indication requirements above) or with compensated cirrhosis: One tablet PO QD for 12 weeks **Genotype 4, 5, 6** Treatment naïve and treatment-experienced, without cirrhosis or with compensated cirrhosis: One tablet PO QD for 12 weeks	1 tablet/day
Epclusa® (sofosbuvir/ velpatasvir)	**Genotype 1 through 6**	1 tablet/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Without cirrhosis or with compensated cirrhosis, treatment naïve or NS3/4A protease inhibitor +/- pegIFN/RBV-experienced: One tablet PO QD for 12 weeks	

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label regimen recommended by AASLD/IDSA HCV guideline, updated March 2021*

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 (DAAs) for Treatment of HCV Infection

Brand Name	Drug Class				
	NS5A Inhibitor	Nucleotide Analog NS5B Polymerase Inhibitor	Non-Nucleoside NS5B Palm Polymerase Inhibitor	NS3/4A Protease Inhibitor (PI)**	CYP3A Inhibitor
Epclusa*	Velpatasvir	Sofosbuvir			
Harvoni*	Ledipasvir	Sofosbuvir			
Mavyret*	Pibrentasvir			Glecaprevir	
Sovaldi		Sofosbuvir			
Viekira PAK*	Ombitasvir		Dasabuvir	Paritaprevir	Ritonavir
Vosevi*	Velpatasvir	Sofosbuvir		Voxilaprevir	
Zepatier*	Elbasvir			Grazoprevir	

**Combination drugs*

Appendix E: General Information

- Acceptable medical justification for inability to use Epclusa or Harvoni (preferred products):
  - In patients indicated for co-administration with ribavirin: contraindications to ribavirin
  - In patients indicated for co-administration with amiodarone: serious symptomatic bradycardia in patients taking amiodarone, with cardiac monitoring recommended
- 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 V on the longer recommended duration of therapy.

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/): 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): 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.
- Clinical Care Options: http://www.clinicaloptions.com/hepatitis.aspx
- CDC training resources: https://www.cdc.gov/hepatitis/resources/professionals/trainingresources.htm

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose	Reference
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	FDA-approved labeling
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	FDA-approved labeling
Genotype 1b: Treatment-naïve or PegIFN/RBV experienced with or without compensated cirrhosis	One tablet PO QD for 12 weeks An 8-week regimen can be considered in those with genotype 1b infection and mild fibrosis (F0-F2)‡	One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day	1) FDA-approved labeling 2) AASLD-IDSA (updated March 2021)
Genotype 1a or 1b: pegIFN/RBV/NS3/4A 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	FDA-approved labeling
Genotype 4: Treatment-naive with or without compensated cirrhosis	One tablet PO QD for 12 weeks	One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day	FDA-approved labeling
Genotype 4: PegIFN/RBV-experienced with or without compensated cirrhosis	One tablet PO QD plus weight-based RBV for 16 weeks	One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day	FDA-approved labeling

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.
** NS3/4A 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

1. Zepatier Prescribing Information. Whitehouse Station, NJ: Merck and Company, Inc.; December 2019. Available at http://www.merck.com/product/usa/pi_circulars/z/zepatier/zepatier_pi.pdf. Accessed February 12, 2021.
2. American Association for the Study of Liver Diseases/ Infectious Disease Society of America (AASLD-IDSA). HCV guidance: recommendations for testing, managing, and treating hepatitis C. Last updated November 6, 2019. Available at: https://www.hcvguidelines.org/. Accessed May 1, 2020.
3. Hsieh YY, Tung SY, Lee K, et al. Routine blood tests to predict liver fibrosis in chronic hepatitis C. World J Gastroenterol. February 28, 2012; 18(8): 746-53. doi: 10.3748/wjg.v18.i8.746.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template. Modified diagnosis requirement for HCV RNA levels from over a six-month period to within the last 6 months; required documentation of resistance-associated polymorphisms for GT1a; added requirement of documentation of NS5A resistance-associated polymorphisms; consolidated appendix D and E into dosing and administration in section V; deleted viral load and adherence requirement in continued therapy section since appropriate full regimen is provided through initial approval duration per specialist feedback to prevent barriers to adherence; added maximum dose requirement, added documentation of positive response to therapy and continuity of care, and removed CIs in section II, added reference column in section V. Safety criteria was applied according to the safety guidance discussed at CPAC and per EPS.PHARM.31. 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.	07.17	08.17
Revised redirection from Harvoni & Sovaldi to Harvoni & Epclusa per 2018 formulary status; Vosevi excluded from redirection due to no overlapping FDA-approved or AASLD-supported indications.	03.20.18	
3Q 2018 annual review: removed requirement for HBV verification; added requirement for documentation of treatment status and if cirrhosis is present, documentation of Child-Pugh A status; expanded duration of treatment required for COC from 30 days to 60 days; required verification of genotype for COC; removed conditional requirement for RBV CI; removed redirection to Vosevi due to different place in therapy; references reviewed and updated.	05.22.18	08.18
3Q 2019 annual review: removed advanced liver disease requirement to align with 2018 AASLD/IDSA hepatitis C treatment guidelines; references reviewed and updated.	05.24.19	08.19
3Q 2020 annual review: 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; references reviewed and updated.	05.08.20	08.20
3Q 2021 annual review: removed criterion for sobriety documentation as AASLD recommends to treat all patients with HCV except those with short life expectancy; included reference to Appendix E with addition of contraindications that would warrant bypassing preferred agents; updated	05.10.21	08.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Appendix B therapeutic alternatives and section V dosing tables; references reviewed and updated.		

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.