

Clinical Policy: Elbasvir/Grazoprevir (Zepatier)

Reference Number: IL.ERX.SPA.132

Effective Date: 06.01.21

Last Review Date: 08.21

Line of Business: Illinois 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-naïve 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 both of the following (a and b):
 - a. Mavyret (e.g., concurrent treatment with efavirenz or atazanavir, Child-Pugh B or C hepatic disease);
 - b. Authorized generic sofosbuvir/velpatasvir (Epclusa®) (e.g., patients in whom ribavirin is contraindicated, concurrent administration with carbamazepine, phenytoin, oxcarbazepine, rifampin, tipranavir/ritonavir);
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	IDSA: Infectious Diseases Society of America
FDA: Food and Drug Administration	NS3/4A, NS5A/B: nonstructural protein
HBV: hepatitis B virus	PegIFN: pegylated interferon
HCC: hepatocellular carcinoma	RBV: ribavirin
HCV: hepatitis C virus	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
sofosbuvir/velpatasvir (Epclusa®)	Genotype 1 or 4: Without cirrhosis or with compensated cirrhosis, treatment-naïve or treatment-experienced* patient One tablet PO QD for 12 weeks	Adult/Peds ≥ 30 kg: sofosbuvir 400 mg /velpatasvir 100 mg (one tablet) per day;
sofosbuvir/velpatasvir (Epclusa®)	Genotype 1 or 4: With decompensated cirrhosis treatment-naïve or treatment-experienced* patient One tablet PO QD with weight-based RBV for 12 weeks (GT 1 or 4 with decompensated cirrhosis and RBV-ineligible may use: one tablet PO QD for 24 weeks)†	Peds 17 to < 30 kg: sofosbuvir 200 mg /velpatasvir 50 mg per day;

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
		Peds < 17 kg: sofosbuvir 150 mg /velpatasvir 37.5 mg per day
sofosbuvir/velpatasvir (Epclusa®)	Genotype 1 or 4: With decompensated cirrhosis in whom prior sofosbuvir- or NS5A-based treatment failed One tablet PO QD with weight-based RBV for 24 weeks [†]	One tablet (sofosbuvir 400 mg /velpatasvir 100 mg) per day
sofosbuvir/velpatasvir (Epclusa®)	Genotype 1b: With compensated cirrhosis or without cirrhosis and non-NS5A inhibitor, sofosbuvir-containing regimen-experienced One tablet PO QD for 12 weeks [†]	One tablet (sofosbuvir 400 mg /velpatasvir 100 mg) per day
Mavyret® (glecaprevir/pibrentasvir)	Genotypes 1 or 4: Treatment-naïve Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 8 weeks	Adults/Peds age ≥ 12 years or with body weight ≥ 45 kg: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) per day;
Mavyret® (glecaprevir/pibrentasvir)	Genotypes 1 or 4: Treatment-experienced with IFN/pegIFN + RBV +/- sofosbuvir infection Without cirrhosis: Three tablets PO QD for 8 weeks With compensated cirrhosis: Three tablets PO QD for 12 weeks	Peds age 3 years to < 12 years of age with body weight < 20 kg: glecaprevir 150 mg/pibrentasvir 60 mg per day;
Mavyret® (glecaprevir/pibrentasvir)	Genotype 1: Treatment-experienced with NS5A inhibitor without prior NS3/4A protease inhibitor Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks	Peds age 3 years to < 12 years of age with body weight 20 kg to < 30 kg: glecaprevir 200 mg/pibrentasvir 80 mg per day;
Mavyret® (glecaprevir/pibrentasvir)	Genotype 1: Treatment-experienced with NS3/4A protease inhibitor without prior NS5A inhibitor Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 12 weeks	Peds age 3 years to < 12 years of age with body weight 30 kg to < 45 kg: glecaprevir 250 mg/pibrentasvir 100 mg per day

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.

* From clinical trials, treatment-experienced refers to previous treatment with NS3/4A protease inhibitor (telaprevir, boceprevir, or simeprevir) and/or peginterferon/RBV unless otherwise stated
 ‡ Off-label, AASLD-IDSA guideline-supported dosing regimen

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 coinfecting 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

- 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.

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-naïve 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 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 April 15, 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 March 12, 2021. Available at: <https://www.hcvguidelines.org/>. Accessed April 15, 2021.
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
Policy created.	04.27.21	05.21
3Q 2021 annual review: removed criterion for sobriety documentation as AASLD recommends to treat all patients with HCV except those with short life expectancy; updated Appendix B therapeutic alternatives and section V dosing tables; references reviewed and updated.	07.16.21	08.21

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.

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