Clinical Policy: Elbasvir/Grazoprevir (Zepatier)

Reference Number: CP.PHAR.275
Effective Date: 09.16
Last Review Date: 08.24
Line of Business: 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 treatment of chronic HCV genotype 1 or 4 infection in adults and pediatrics patients 12 years of age and older or weighing at least 30 kg. Zepatier is indicated for use with ribavirin (RBV) 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*

For members in **Nevada, medical management techniques, including quantity management, beyond step therapy is not allowed.*

A. Hepatitis C Infection (must meet all)**:**

1. Diagnosis of HCV infection as evidenced by detectable serum HCV RNA levels by quantitative assay in the last 6 months;
2. Age ≥ 12 years or weight ≥ 30 kg;
3. Confirmed HCV genotype is 1 or 4;
   **Chart note documentation and copies of lab results are required*
4. 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;
5. Documentation of the treatment status of the patient (treatment-naive or treatment-experienced);
6. If cirrhosis is present, confirmation of Child-Pugh A status;
7. Member must use **Mavyret®** or **sofosbuvir/velpatasvir (Epclusa® authorized generic)**, unless clinically significant adverse effects are experienced or both are contraindicated (*see Appendix E*);*
   ** Coadministration with omeprazole up to 20 mg is not considered acceptable medical justification for inability to use Epclusa*
8. Life expectancy ≥ 12 months with HCV treatment;
9. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see Section V Dosage and Administration for reference)*;

10. 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 (must meet all)**:**

1. Member must use **Mavyret** or **sofosbuvir/velpatasvir (Epclusa authorized generic**), if applicable for the requested indication, unless clinically significant adverse effects are experienced or both are contraindicated (*see Appendix E*);*
   ** Coadministration with omeprazole up to 20 mg is not considered acceptable medical justification for inability to use Epclusa*
2. One of the following (a or b):
   a. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (i or ii):
      i. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
      ii. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
   b. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 2a above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

II. Continued Therapy*

For members in **Nevada, medical management techniques, including quantity management, beyond step therapy is not allowed.*

A. Hepatitis C Infection (must meet all)**:**

1. Member meets one of the following (a, b, or c):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
   c. Both of the following (i and ii):
      i. Documentation supports that member is currently receiving Zepatier for 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 (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

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 policies – CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AASLD: American Association for the Study of Liver Diseases
DAA: direct-acting antiviral
FDA: Food and Drug Administration
HBV: hepatitis B virus
HCV: hepatitis C virus
HIV: human immunodeficiency virus
IDSA: Infectious Diseases Society of America
NS3/4A, NS5A/B: nonstructural protein
PegIFN: pegylated interferon
RBV: ribavirin
RNA: ribonucleic acid
SVR12: sustained virologic response at 12 weeks

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 for all relevant lines of business 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	One tablet (sofosbuvir 400 mg /velpatasvir 100 mg) per day
Mavyret® (glecaprevir /pibrentasvir)	**Genotypes 1 or 4:** Treatment-naïve	Mavyret: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) per day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 8 weeks	
Mavyret® (glecaprevir /pibrentasvir)	**Genotypes 1 or 4:** Treatment-experienced with IFN/pegIFN, RBV, and/or sofosbuvir Without cirrhosis: Three tablets PO QD for 8 weeks With compensated cirrhosis: Three tablets PO QD for 12 weeks	Mavyret: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) 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	Mavyret: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) 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*
† In Mavyret clinical trials, subjects were treated with prior regimens containing ledipasvir and sofosbuvir or daclatasvir with (peg)interferon and RBV

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 or those with any history of hepatic decompensation due to the risk of hepatic decompensation.
  - 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 (HBV) reactivation in patients coinfected with HCV and HBV.

Appendix D: Direct-Acting Antivirals 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

- Unacceptable medical justification for inability to use Epclusa (preferred product):
  - Coadministration with omeprazole up to 20 mg is not considered acceptable medical justification for inability to use Epclusa.
    - Per the Epclusa Prescribing Information: "If it is considered medically necessary to coadminister, Epclusa should be administered with food and taken 4 hours before omeprazole 20 mg."
- Acceptable medical justification for inability to use Epclusa (preferred product):
  - In patients indicated for co-administration of Epclusa with ribavirin: contraindications to ribavirin.
  - In patients indicated for co-administration with amiodarone: serious symptomatic bradycardia in patients taking amiodarone, with cardiac monitoring recommended.
- HBV reactivation 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.
- Child-Pugh Score:

	1 Point	2 Points	3 Points
Bilirubin	Less than 2 mg/dL Less than 34 umol/L	2-3 mg/dL 34-50 umol/L	Over 3 mg/dL Over 50 umol/L
Albumin	Over 3.5 g/dL	2.8-3.5 g/dL	Less than 2.8 g/dL

	1 Point	2 Points	3 Points
	Over 35 g/L	28-35 g/L	Less than 28 g/L
INR	Less than 1.7	1.7 - 2.2	Over 2.2
Ascites	None	Mild / medically controlled	Moderate-severe / poorly controlled
Encephalopathy	None	Mild / medically controlled Grade I-II	Moderate-severe / poorly controlled. Grade III-IV

Child-Pugh class is determined by the total number of points: A = 5-6 points; B = 7-9 points; C = 10-15 points.

Appendix F: Incomplete Adherence and AASLD-IDSA Recommended Management of Treatment Interruptions

- There are minimal data regarding the outcome of patients who have incomplete adherence to direct-acting antiviral (DAA) therapy or the threshold level of adherence below which the incidence of sustained virologic response at 12 weeks (SVR12) is significantly reduced. In general, a treatment interruption of < 7 days is unlikely to impact SVR12.
- There are few data on which to base recommendations regarding how to manage patients who have discontinued DAAs for several days to weeks. The below recommendations are applicable to treatment-naive patients with HCV, without cirrhosis or with compensated cirrhosis*, receiving either Mavyret or Epclusa*. Patients with prior DAA treatment, or receiving other DAA treatment regimens, or other populations (e.g., patients who are posttransplant or have decompensated cirrhosis) should be managed in consultation with an expert.
  - Interruptions during the first 28 days of DAA therapy:
    - If missed ≤ 7 days, restart DAA therapy immediately and complete therapy for originally planned duration (8 or 12 weeks).
    - If missed ≥ 8 days, restart DAA therapy immediately and obtain HCV RNA test as soon as possible. If HCV RNA is negative, complete originally planned DAA treatment course (8 or 12 weeks). Recommendation to extend DAA treatment for an additional 4 weeks for patients with genotype 3 and/or cirrhosis. If HCV RNA is positive or not obtained, extend DAA treatment for an additional 4 weeks.
  - Interruptions after receiving ≥ 28 days of DAA therapy:
    - If missed ≤ 7 days, restart DAA therapy immediately and complete therapy for originally planned duration (8 or 12 weeks).
    - If missed 8-20 consecutive days, restart DAA therapy immediately and obtain HCV RNA test as soon as possible. If HCV RNA is negative, complete originally planned DAA treatment course (8 or 12 weeks). Recommendation to extend DAA treatment for an additional 4 weeks for patients with genotype 3 and/or cirrhosis. If HCV RNA is positive or not obtained, stop treatment and retreat according to the recommendations in the AASLD-IDSA Retreatment Section.
    - If missed ≥ 21 consecutive days, stop DAA treatment and assess for SVR12. If SVR12 not achieved, retreat according to the recommendations in the AASLD-IDSA Retreatment Section.

V. Dosage and Administration

Indication: HCV	Dosing Regimen	Maximum Dose	Reference
Genotype 1a: Treatment-naïve or pegIFN/RBV-experienced with or without compensated cirrhosis and 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 and 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 December 2023)
Genotype 1a or 1b: pegIFN/RBV/NS3/4A PI* - experienced with or without compensated cirrhosis, (for genotype 1a: 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 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*
ǂ 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.; May 2022. Available at: http://www.merck.com/product/usa/pi_circulars/z/zepatier/zepatier_pi.pdf. Accessed April 6, 2024.
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 December 19, 2023. Available at: https://www.hcvguidelines.org/. Accessed May 20, 2024.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2020 annual review: added SDC re-direction to preferred Mavyret or Eplcusa authorized generic; Appendix B therapeutic alternative regimens table added; references reviewed and updated.	04.30.20	08.20
2Q 2021 annual review: removed reference to appendix B for consistency with other HCV policies; updated dosing in section V to be consistent with PI; references reviewed and updated.	02.14.21	05.21
3Q 2021 annual review: no significant changes; included reference to Appendix E with the addition of un/acceptable rationale for bypassing preferred agents; updated Appendix B therapeutic alternatives; references reviewed and updated.	05.08.21	08.21
RT4: added pediatric use extension to 12 years of age and older or weight at least 30 kg.	01.13.22	
3Q 2022 annual review: no significant changes; added omeprazole coadministration as unacceptable rationale for not using preferred Epclusa and removed redundant rationale in Appendix E and criteria; references reviewed and updated.	07.20.22	08.22
Template changes applied to other diagnoses/indications and continued therapy section.	09.20.22	
3Q 2023 annual review: removed prescriber specialty criterion per Medicaid plan requests; eliminated adherence program participation criterion due to competitor analysis; added redirections to other diagnoses initial criteria section; references reviewed and updated.	05.31.23	08.23
Added disclaimer that medical management techniques, including quantity management, beyond step therapy are not allowed for members in NV per SB 439.	05.31.24	
3Q 2024 annual review: removed qualifier of "chronic" from HCV criteria as AASLD-IDSA recommends treatment of both acute and	05.30.24	08.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
chronic HCV; removed "preferred" from Epclusa authorized generic redirection; added Appendix F for guidance on incomplete adherence and AASLD-IDSA recommended management of treatment interruptions; 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. 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.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.