Clinical Policy: Elbasvir/Grazoprevir (Zepatier)

Reference Number: GA.PMN.16
Effective Date: 12/16
Last Review Date: 7/2023 Revision Log
Line of Business: Medicaid

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Elbasvir/Grazoprevir (Zepatier®/™) is a fixed-dose combination of grazoprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and elbasvir, an HCV NS5A inhibitor.

FDA Approved Indication(s)
Epclusa is indicated for the treatment of adult patients with chronic HCV
- Genotype 1 or 4 infection in adults
- In combination with ribavirin in certain patient populations

Policy/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
*** Provider must submit documentation (including office chart notes and lab results) supporting that member has met all approval criteria ***

A. Chronic Hepatitis C Infection (must meet all)**:**
1. Diagnosis of chronic hepatitis C virus (HCV) infection as evidenced by detectable HCV RNA (ribonucleic acid) levels 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 labs 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-naïve or treatment-experienced);
6. Documentation of cirrhosis status of the patient (no cirrhosis, compensated cirrhosis, or decompensated cirrhosis);
7. Member must use **Mavyret® or sofosbuvir/velpatasvir (Epclusa®) (*authorized generic preferred*),** 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 III Dosage and Administration for reference)*;
10. Member is hepatitis B virus (HBV) negative, or if positive, documentation that concurrent HBV infection is being treated (e.g., tenofovir alafenamide, adefovir, entecavir), unless contraindicated or clinically significant adverse effects are experienced (*see Appendix E*);
11. Member has none of the following contraindications:
    a. Moderate to severe hepatic impairment (Child-Pugh B and C);
    b. Co-administration with efavirenz or organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors or strong inducers of CYP 450 (CYP3A) including: phenytoin, carbamazepine, rifampin, St. John's Wort, atazanavir, darunavir, lopinavir, saquinavir, tipranavir, cyclosporine;
    c. If prescribed with ribavirin, member has none of the following contraindications:
        i. Pregnancy or possibility of pregnancy - member or partner;
        ii. Hypersensitivity to ribavirin;
        iii. Coadministration with didanosine;
        iv. Significant/unstable cardiac disease;
        v. Hemoglobinopathy (e.g., thalassemia major, sickle cell anemia);
        vi. Hemoglobin < 8.5 g/dL.

Approval duration: up to a total of 16 weeks*
*(*Approved duration should be consistent with a regimen in Section III Dosage and Administration)*

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Member must use **Mavyret** or **sofosbuvir/velpatasvir (Epclusa) (*authorized generic preferred*)** 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. Appendix A: Abbreviation/Acronym Key

AASLD: American Association for the Study of Liver Diseases
APRI: AST to platelet ratio
CTP: Child Turcotte Pugh
CrCl: creatinine clearance
FDA: Food and Drug Administration
FIB-4: Fibrosis-4 index
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
IDSA: Infectious Diseases Society of America
MRE: magnetic resonance elastography
NS3/4A, NS5A/B: nonstructural protein
Peg-IFN: pegylated interferon
PI: protease inhibitor
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 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 pegIFN/ RBV-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 Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 8 weeks	Mavyret: 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	Mavyret: glecaprevir 300 mg/pibrentasvir 120 mg (3 tablets) per day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	With compensated cirrhosis: Three tablets PO QD for 12 weeks	
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.
**Treatment-experienced refers to previous treatment with NS3 protease inhibitor (telaprevir, boceprevir, or simeprevir) and/or peginterferon/RBV unless otherwise stated*
ǂ *Off-label, AASLD-IDSA guideline-supported dosing regimen*

Appendix C: Contraindications

- Zepatier is contraindicated in:
  - 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 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
Daklinza	Daclatasvir				
Epclusa*	Velpatasvir	Sofosbuvir			
Harvoni*	Ledipasvir	Sofosbuvir			

Brand Name	Drug Class				
	NS5A Inhibitor	Nucleotide Analog NS5B Polymerase Inhibitor	Non-Nucleoside NS5B Palm Polymerase Inhibitor	NS3/4A Protease Inhibitor (PI)**	CYP3A Inhibitor
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 Mavyret (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."

  - Drug-drug interactions with one or more of the following agents:
    - Rifampin, efavirenz, atazanavir, carbamazepine, or St. John's wort:
    - These drug-drug interactions are not unique to Mavyret, and several apply across the entire therapeutic class of direct-acting antivirals for treatment of HCV infection.
    - The combination of either efavirenz or atazanavir with either Mavyret or Zepatier should be avoided per most recent AASLD/IDSA HCV guidance (March 2021).
- 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.
- Hepatitis B Virus (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 VI 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 Over 35 g/L	2.8-3.5 g/dL 28-35 g/L	Less than 2.8 g/dL 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.*

III. 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	1) FDA-approved labeling 2) AASLD-IDSA (updated November 2019)
Genotype 1a: Treatment-naïve or PegIFN/RBV experienced with or without compensated cirrhosis with baseline NS5A	One tablet PO QD plus weight-based RBV for 16 weeks	One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day	1) FDA-approved labeling 2) AASLD-IDSA (updated November 2019)

Indication	Dosing Regimen	Maximum Dose	Reference
polymorphisms at amino acid positions 28, 30, 31, or 93			
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)ǂ	One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day	1) FDA-approved labeling 2) AASLD-IDSA (updated November 2019)
Genotype 1a or 1b: pegIFN/RBV/NS3/4a PI*ǂ -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	1) FDA-approved labeling 2) AASLD-IDSA (updated November 2019)
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	1) FDA-approved labeling 2) AASLD-IDSA (updated November 2019)
Genotype 4: PegIFN/RBV-experienced with or without compensated cirrhosis with virologic relapse/failure	Virologic relapse after prior pegIFN/RBV therapy: One tablet PO QD for 12 weeks Virologic failure while on pegIFN/RBV therapy: One tablet PO QD plus weight-based RBV for 16 weeks	One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day	1) 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.
*Treatment-experienced refers to previous treatment with NS3/4a protease inhibitor (telaprevir, boceprevir, or simeprevir) and/or peginterfon/RBV unless otherwise stated
ǂOff-label, AASLD-IDSA guideline-supported dosing regimen

IV. Product Availability

Tablet: elbasvir 50mg with grazoprevir 100mg

V. 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 20, 2023.
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 October 24, 2022. Available at: https://www.hcvguidelines.org/. Accessed May 5, 2023.
3. CDC. Hepatitis C Q&As for health professionals. Last updated August 7, 2020. Available at: https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm. Accessed May 5, 2023.

Reviews, Revisions, and Approvals	Date	Approval Date
New policy created, split from CP.PHAR.17 Hepatitis C Therapies. HCV RNA levels over six-month period added to confirm infection is chronic. Life expectancy "≥12 months if HCC and awaiting transplant" is modified to indicate "≥12 months with HCV therapy". Testing criteria reorganized by "no cirrhosis"/"cirrhosis" consistent with the regimen tables; HCC population is included under "cirrhosis" and broadened to incorporate HCC amenable to curative measures (resection, ablation, transplant). Methods to diagnose fibrosis/cirrhosis are modified to require presence of HCC, liver biopsy or a combination of one serologic and one radiologic test. Serologic and radiologic tests are updated and correlated with METAVIR per Appendix B. Removed creatinine clearance restriction. Criteria added excluding post-liver transplantation unless regimens specifically designate. Dosing regimens are presented in Appendix D and E per AASLD guidelines and FDA-approved indications. The initial approval is shortened to 8 weeks.	08/16	09/16
Removed criteria regarding medication prescribed by a specialist Remove criteria regarding having HCC or advanced liver disease Removed criteria regarding medication adherence program Removed criteria regarding sobriety from alcohol/illicit drugs	10/16	10/2016
Added availability of full course of therapy as initial therapy consistent with appendix recommendation for initial criteria Removed continuation criteria	4/17	4/17
Added requirement of documentation of NS5A resistance-associated polymorphisms. Added preferencing information requiring Mavyret for FDA-approved indications. Added requirement for 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.	9/17	9/17
Annual review. No changes made.	3/18	3/18

Reviews, Revisions, and Approvals	Date	Approval Date
Changed current Georgia policy templates to corporate standard templates for drug coverage criteria to meet corporate compliance. Changes/revisions included; new formatting, font size, use of standard policy language for each section of policy, and rearranged order of certain steps in criteria and sections. Added new preferred treatment tables that includes dosage and frequency based on genotype for Mavyret. Removed background sections. Updated general information and contraindication section to be consistent with corporate HCV policies.	2/21/19	2/19
Annual review. In the initial approval criteria, changed RNA detectable period from "over a 6 month period" to "in the last 6 months" for infection diagnosis.	10/19	10/19
Removed redirection to Mavyret based on contraindications criteria and all other information relative to Mavyret. Removed Appendix C for Metavir scoring. Updated order of all other Appendices. Updated references.	4/2020	4/2020
Added re-direction to preferred Mavyret or Eplcusa authorized generic; Appendix B therapeutic alternative regimens table added; references reviewed and updated.	7/2020	7/2020
Annual review. Added hepatitis B box warning to Appendix B Contraindications. Removed reference to appendix B for consistency with other HCV policies; updated dosing in section III to be consistent with PI Added Mayvret and Vosevi to Appendix D-Direct Acting Antivirals for Treatment of HCV infection and removed Olysio, Technivie, and Viekira XR as these were previously removed from the market. Added an additional tablet strength under product availability. Changed Centene Logo to PSHP Logo. References reviewed and updated.	4/2021	4/2021
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.	7/2021	7/2021
3Q 2022 annual review. added omeprazole coadministration as unacceptable rationale for not using preferred Epclusa, removed redundant rationale and black box warnings, removed precaution of concurrent anticoagulation therapy as it is a caution and not an absolute contraindication in Appendix E; References reviewed and updated.	7/2022	7/2022
Added omeprazole coadministration as unacceptable rationale for not using preferred Epclusa to criteria. Minor font updates.	10/2022	10/2022
Template changes applied to other diagnoses/indications.	1/2023	1/2023
Added pediatric use extension to 12 years of age and older or weight at least 30 kg.	4/2023	4/2023
3Q 2023 annual review. Added redirections to other diagnoses initial criteria section; references reviewed and updated.	7/2023	7/2023

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.