Clinical Policy: Elbasvir/Grazoprevir (Zepatier)

Reference Number: GA.PMN.16
Effective Date: 12/16
Last Review Date: 7/2020 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 ≥ 18 years;
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 B for HCV status-specific regimens*);
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: Refer to CP.PHAR.53 – No Coverage Criteria/Off-Label Use Policy if diagnosis is NOT specifically listed under section I.

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
Epclusa® (sofosbuvir/ velpatasvir)	**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
Epclusa® (sofosbuvir/ velpatasvir)	**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)‡	One tablet (sofosbuvir 400 mg /velpatasvir 100 mg) per day
Epclusa® (sofosbuvir/ velpatasvir)	**Genotype 1 or 4:** With decompensated cirrhosis in whom prior sofosbuvir- or NS5A-based treatment experienced failed One tablet PO QD with weight-based RBV for 24 weeks‡	One tablet (sofosbuvir 400 mg /velpatasvir 100 mg) per day
Epclusa® (sofosbuvir/ velpatasvir)	**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	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)	**Genotypes 1 or 4:** Treatment-experienced with 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 NS5A inhibitor without prior NS3/4A protease inhibitor Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 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.
**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.

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			
Olysio				Simeprevir	
Sovaldi		Sofosbuvir			
Technivie*	Ombitasvir			Paritaprevir	Ritonavir
Viekira XR/PAK*	Ombitasvir		Dasabuvir	Paritaprevir	Ritonavir
.Zepatier*	Elbasvir			Grazoprevir	

*Combination drugs

Appendix E: General Information

- 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.

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 May 2018)

Indication	Dosing Regimen	Maximum Dose	Reference
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	1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)
Genotype 1b: Treatment-naïve or PegIFN/RBV experienced 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 May 2018)
Genotype 1a or 1b: pegIFN/RBV/NS3 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	1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)
Genotype 1a or 1b: pegIFN/RBV/NS3 PI*‡ -experienced with or without compensated cirrhosis with baseline NS5A polymorphisms at	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 May 2018)

Indication	Dosing Regimen	Maximum Dose	Reference
amino acid positions 28, 30, 31, or 93			
Genotype 3ǂ: pegIFN/RBV-experienced with compensated cirrhosis	One tablet PO QD plus sofosbuvir 400 mg for 12 weeks	One tablet (grazoprevir 100 mg/ elbasvir 50 mg) per day	1) FDA-approved labeling 2) AASLD-IDSA (updated May 2018)
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 May 2018)
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	AASLD-IDSA (updated September 2017)

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 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

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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	08/16	09/16

Reviews, Revisions, and Approvals	Date	Approval Date
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.		
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
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

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.

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.