

**Clinical Policy: Elbasvir/Grazoprevir (Zepatier)**

Reference Number: LA.PHAR.275

Effective Date: 09/16

Last Review Date: 07/18

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<sup>®</sup>) 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**

Zepatier is indicated for 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 (including office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> 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 multiple detectable HCV RNA (ribonucleic acid) levels in the last 6 months;
2. Confirmed HCV genotype is 1 or 4;
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 patient (treatment-naive or treatment-experienced);
5. If cirrhosis is present, confirmation of Child-Pugh A status;
6. Age  $\geq$  18 years;
7. Member is contraindicated to treatment with Mavyret due to current treatment with efavirenz or atazanavir;  
*\*See Appendix F for additional details on acceptable contraindications*
8. Life expectancy  $\geq$  12 months with HCV treatment;
9. Documented sobriety from alcohol and illicit IV drugs for  $\geq$  6 months prior to starting therapy, if applicable;
10. Advanced liver disease defined as (a,b or c):
  - a. Advanced fibrosis indicated by i, ii, or iii:
    - i. Liver biopsy showing a METAVIR score of F3 or equivalent (Knodell, Scheuer, Batts-Ludwig – F3; Ishak – F4/5);

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- ii. One serologic test showing an equivalent score to METAVIR F3
  - iii. One radiologic test showing an equivalent score to METAVIR F3 per Appendix C;
  - b. Cirrhosis indicated by i, ii, iii, iv or v:
    - i. Hepatocellular carcinoma (HCC) amenable to resection, ablation or transplant;
    - ii. Liver biopsy showing a METAVIR score of F4 or equivalent (Knodell, Scheuer, Batts-Ludwig – F4; Ishak - F5/6);
    - iii. One serologic test showing an equivalent score to METAVIR F4 per Appendix C;
    - iv. One radiologic test showing an equivalent score to METAVIR F4 per Appendix C;
    - v. Other radiologic test showing evidence of cirrhosis (e.g., portal hypertension);
  - c. If member is HIV/HCV co-infected, there shall be no METAVIR score requirements.
11. Prescribed regimen is consistent with an FDA or AASLD-IDSAs recommended regimen (*see Section V Dosage and Administration for reference*);
12. Dose does not exceed elbasvir/grazoprevir 50 mg/100 mg (1 tablet) per day.

**Approval duration: up to 16 weeks\***

(\*Approved duration should be consistent with a regimen in Section V Dosage and Administration)

**B. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

**II. Continued Therapy****A. Chronic Hepatitis C Infection** (must meet all):

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Zepatier for chronic hepatitis C virus infection and has received this medication for at least 60 days;
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 the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid

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**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*

ALT: alanine aminotransferase	HCV: hepatitis C virus
APRI: AST to platelet ratio	IDSA: Infectious Diseases Society of America
AASLD: American Association for the Study of Liver Diseases	MRE: magnetic resonance elastography
FDA: Food and Drug Administration	NS3/4A, NS5A/B: nonstructural protein
FIB-4: Fibrosis-4 index	Peg-IFN: pegylated interferon
HBeAg: hepatitis B virus envelope antigen	PI: protease inhibitor
HBV: hepatitis B virus	RBV: ribavirin
HCC: hepatocellular carcinoma	ULN: upper limit of normal

*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.*

<b>Drug Name</b>	<b>Dosing Regimen</b>	<b>Dose Limit/ Maximum Dose</b>
Mavyret™ (glecaprevir/ pibrentasvir)	Treatment-naïve chronic HCV infection: <b>Genotypes 1 or 4</b>  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)	Treatment-experienced with IFN/pegIFN + RBV +/- sofosbuvir chronic HCV infection: <b>Genotypes 1, 3, or 4</b>  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

*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.*

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*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: Approximate Scoring Equivalencies using METAVIR F3/F4 as Reference*

Fibrosis/ Cirrhosis	Serologic Tests*				Radiologic Tests†		Liver Biopsy‡	
	Fibro Test	FIBRO Spect II	APRI	FIB-4	FibroScan (kPa)	MRE (kPa)	METAVIR	Ishak
Advanced fibrosis	≥0.59	≥42	>1.5	>3.25	≥9.5	≥4.11	F3	F4-5
Cirrhosis	≥0.75	≥42	>1.5	>3.25	≥12.0	≥4.71	F4	F5-6

\*Serologic tests:

- FibroTest (available through Quest as FibroTest or LabCorp as FibroSure)
- FIBROSpect II (available through Prometheus Laboratory)
- APRI (AST to platelet ratio index)
- FIB-4 (Fibrosis-4 index: includes age, AST level, platelet count)

†Radiologic tests:

- FibroScan (transient elastography)
- MRE (magnetic resonance elastography)

‡Liver biopsy (histologic scoring systems):

- METAVIR F3/F4 is equivalent to Knodell, Scheuer, and Batts-Ludwig F3/F4 and Ishak F4-5/F5-6
- METAVIR fibrosis stages: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = few septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis

*Appendix E: 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			
Mavyret*	Pibrentasvir			Glecaprevir	
Olysio				Simeprevir	
Sovaldi		Sofosbuvir			
Technivie*	Ombitasvir			Paritaprevir	Ritonavir
Viekira XR/PAK*	Ombitasvir		Dasabuvir	Paritaprevir	Ritonavir
Vosevi*	Velpatasvir	Sofosbuvir		Voxilaprevir	

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

\*Combination drugs

*Appendix F: 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.
- According to the September 2017 AASLD/IDSA HCV guidance updates, Zepatier plus Sovaldi is a recommended treatment option for patients treatment-experienced with pegIFN/RBV with compensated cirrhosis and genotype 3.
- Child-Pugh Score:

	1 Point	2 Points	3 Points
Bilirubin	<i>Less than 2 mg/dL Less than 34 umol/L</i>	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.

- Acceptable medical justification for inability to use Mavyret (preferred product):
  - Severe hepatic disease (Child-Pugh C): use of Mavyret is not recommended due to higher exposures of glecaprevir and pibrentasvir.
  - Moderate hepatic disease (Child-Pugh B): although not an absolute contraindication, use of Mavyret is not recommended in patients with moderate hepatic disease (Child-Pugh B) due to lack of safety and efficacy data.
    - Following administration of Mavyret in HCV infected subjects with *compensated* cirrhosis (Child-Pugh A), exposure of glecaprevir was

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- approximately 2-fold and pibrentasvir exposure was similar to non-cirrhotic *HCV infected* subjects.
  - At the clinical dose, compared to *non-HCV infected* subjects with *normal hepatic function*, glecaprevir AUC was 100% higher in Child-Pugh B subjects, and increased to 11-fold in Child-Pugh C subjects. Pibrentasvir AUC was 26% higher in Child-Pugh B subjects, and 114% higher in Child-Pugh C subjects.
- Drug-drug interactions with one or more the following agents:
  - Atazanavir
  - Efavirenz
- Unacceptable medical justification for inability to use Mavyret (preferred product):
  - Black Box Warning (BBW): currently or previously infected with hepatitis B virus. This BBW is not unique to Mavyret, and it applies across the entire therapeutic class of direct-acting antivirals for treatment of HCV infection. Therefore it is not a valid clinical reason not to use Mavyret.
  - Concurrent anticoagulant therapy: Fluctuations in International Normalized Ratio (INR) have been observed in warfarin recipients who were also receiving treatment for HCV infections. This BBW is not unique to Mavyret, and it applies across the entire therapeutic class of direct-acting antivirals for treatment of HCV infection. Although caution is advised when using Mavyret while receiving concurrent anticoagulant therapy, specifically warfarin, this is not an absolute contraindication as long as patient is adequately monitored and educated during therapy.
  - Drug-drug interactions with one or more of the following agents:
    - Rifampin, carbamazepine, or St. John’s wort:
    - These drug-drug interactions are not unique to Mavyret, and they apply across the entire therapeutic class of direct-acting antivirals for treatment of HCV infection.

**V. Dosage and Administration**

Indication	Dosing Regimen	Maximum Dose	Reference
Genotype 1a: Treatment-naïve or PegIFN/RBVexperienced 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	Zepatier (grazoprevir 100 mg /elbasvir 50mg): 1 tablet per day	1) FDA-approved labeling 2) AASLD-IDSA (updated 04/17)
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	Zepatier (grazoprevir 100 mg /elbasvir 50mg): 1 tablet per day	1) FDA-approved labeling 2) AASLD-IDSA (updated 04/17)

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Indication	Dosing Regimen	Maximum Dose	Reference
Genotype 1b: Treatment-naïve or PegIFN/RBV experienced	One tablet PO QD for 12 weeks	Zepatier (grazoprevir 100 mg /elbasvir 50mg): 1 tablet per day	1) FDA- approved labeling 2) AASLD- IDSA (updated 04/17)
Genotype 1a or 1b: PegIFN/RBV/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	Zepatier (grazoprevir 100 mg /elbasvir 50mg): 1 tablet per day	1) FDA- approved labeling 2) AASLD- IDSA (updated 04/17)
Genotype 1a or 1b: PegIFN/RBV/NS3 PI*±- 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	Zepatier (grazoprevir 100 mg /elbasvir 50mg): 1 tablet per day	1) FDA- approved labeling 2) † AASLD- IDSA (updated 04/17)
Genotype 4: Treatment-naïve with or without compensated cirrhosis	One tablet PO QD for 12 weeks	Zepatier (grazoprevir 100 mg /elbasvir 50mg): 1 tablet per day	1) FDA- approved labeling 2) AASLD- IDSA (updated 04/17)
Genotype 4: PegIFN/RBV-experienced with or without compensated cirrhosis with virologic relapse without prior on-treatment virologic failure	One tablet PO QD for 12 weeks	Zepatier (grazoprevir 100 mg /elbasvir 50mg): 1 tablet per day	AASLD-IDSA (updated 04/17)
Genotype 4: PegIFN/RBV-experienced with or without compensated cirrhosis with virologic relapse with prior on-treatment virologic failure	One tablet PO QD plus weight- based RBV for 16 weeks	Zepatier (grazoprevir 100 mg /elbasvir 50mg): 1 tablet per day	1) FDA- approved labeling 2) AASLD- IDSA (updated 04/17)

\*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.

† Off-label, AASLD-IDSA guideline-supported dosing regimen

**VI. Product Availability**

Tablets: grazoprevir 100 mg/elbasvir 50 mg

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**I. 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 population is included under “cirrhosis” and broadened to incorporate HCC amenable to curative measures (resection, ablation,	08/16	09/16



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<p>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.</p> <p>Dosing regimens are presented in Appendix D and E per AASLD guidelines and FDA-approved indications. The initial approval is shortened to 8 weeks.</p>		
<p>Policy converted to new template. Added requirement of documentation of NS5A resistance-associated polymorphisms; added requirement for prevention of HBV reactivation. Consolidated appendix D and E into dosing and administration in section V; deleted viral load and adherence requirement in continued therapy section; 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. Added preferencing information requiring Mavyret for FDA-approved indications.</p> <p>Safety criteria was applied according to the safety guidance discussed at CPAC and endorsed by Centene Medical Affairs. 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.</p>	08/17	09/17
<p>Due to State requirements, removed prescriber restrictions regarding who can prescribe Hepatitis C DAA agents;</p> <p>Removed the abstinence period of 6 months and added documentation required that member is not actively participating in alcohol and/or illicit IV drugs use,;</p> <p>Added statement for NO Fibrosis score required for HIV/HCV co-infected members</p> <p>Changed language to one serologic test OR one radiologic test from one serologic test and one radiologic test</p>	5/18	5/18

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Reviews, Revisions, and Approvals	Date	Approval Date
3Q 2018 annual review: removed requirement for HBV verification; expanded duration of tx required for COC from 30 days to 60 days; required verification of genotype for COC; removed conditional requirement for RBV CI; references reviewed and updated.	07.18	07.18

**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.

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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.

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**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.

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