Clinical Policy: Glecaprevir/Pibrentasvir (Mavyret)

Reference Number: CP.CPA.285
Effective Date: 08.15.17
Last Review Date: 08.21
Line of Business: Commercial

Revision Log

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

Description

Glecaprevir and pibrentasvir (Mavyret®) are a fixed-dose combination of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor.

FDA Approved Indication(s)

Mavyret is indicated for the treatment of adult and pediatric patients 3 years and older with:

- Chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A)
- HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor* or an NS3/4A protease inhibitor**, but not both

* In clinical trials, prior NS5A inhibitor experience included ledipasvir and sofosbuvir or daclatasvir with pegylated interferon and ribavirin.
** In clinical trials, prior NS3/4A protease inhibitor experience included regimens containing simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin.

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 Mavyret 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 serum HCV RNA levels by quantitative assay in the last 6 months;
2. Confirmed HCV genotype is one of the following (a, b, c, or d);
   a. For treatment-naïve patients: genotypes 1, 2, 3, 4, 5, or 6;
   b. For patients treatment-experienced with interferon (IFN)/pegylated-interferon (pegIFN), ribavirin (RBV), and/or sofosbuvir only: genotypes 1, 2, 3, 4, 5, or 6;
   c. For patients treatment-experienced with either an NS5A inhibitor or an NS3/4A protease inhibitor: genotype 1 (*see Appendix D*);
   d. For Vosevi-experienced members and request is for use in combination with sofosbuvir: genotype 1, 2, 3, 4, 5, or 6;

**Chart note documentation and copies of lab results are required*

3. Prescribed by or in consultation with a gastroenterologist, hepatologist, infectious disease specialist, or provider who has expertise in treating HCV based on a certified training program (*see Appendix F*);
4. Age ≥ 3 years;
5. If cirrhosis is present, confirmation of Child-Pugh A status;
6. Member is not treatment-experienced with both NS3/4A protease inhibitor AND NS5A inhibitors, such as combination therapies including Technivie™, Viekira®, and Zepatier®;
7. Member must use brand Epclusa® or Vosevi®, unless clinically significant adverse effects are experienced or all are contraindicated;
8. Life expectancy ≥ 12 months with HCV treatment;
9. Member agrees to participate in a medication adherence program meeting both of the following components (a and b):
   a. Medication adherence monitored by pharmacy claims data or member report;
   b. Member's risk for non-adherence identified by adherence program or member/prescribing physician follow-up at least every 4 weeks;
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 one of the following (a, b, c, or d):
    a. Adult and pediatric members 12 years of age and older or with body weight ≥ 45 kg: glecaprevir 300 mg and pibrentasvir 120 mg (3 tablets) per day;
    b. Pediatric members 3 years to < 12 years of age with body weight < 20 kg: glecaprevir 150 mg and pibrentasvir 60 mg per day;
    c. Pediatric members 3 years to < 12 years of age with body weight 20 kg to < 30 kg: glecaprevir 200 mg and pibrentasvir 80 mg per day;
    d. Pediatric members 3 years to < 12 years of age with body weight 30 kg to < 45 kg: glecaprevir 250 mg and pibrentasvir 100 mg 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.CPA.09 for commercial.

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 Centene benefit or member has previously met initial approval criteria;
   b. Must meet both of the following (i and ii):
      i. Documentation supports that member is currently receiving Mavyret for chronic HCV infection and has recently completed at least 40 days of treatment with Mavyret;
      ii. Confirmed HCV genotype is one of the following (1, 2, 3, or 4);
         1) For treatment-naïve members: genotypes 1, 2, 3, 4, 5, or 6;

2) For members treatment-experienced with interferon (IFN)/pegylated-interferon (pegIFN), ribavirin (RBV), and/or sofosbuvir only: genotypes 1, 2, 3, 4, 5, or 6;
3) For members treatment-experienced with either an NS5A inhibitor or an NS3/4A protease inhibitor: genotype 1 (*see Appendix E*);
4) For Vosevi-experienced members: genotype 1, 2, 3, 4, 5, or 6;

2. Member is not treatment-experienced with both NS3/4A protease inhibitor AND NS5A inhibitors, such as combination therapies including Technivie, Viekira, and Zepatier;
3. Member is responding positively to therapy;
4. Dose does not exceed one of the following (a, b, c, or d):
   a. Adult and pediatric members 12 years of age and older or with body weight ≥ 45 kg: glecaprevir 300 mg and pibrentasvir 120 mg (3 tablets) per day;
   b. Pediatric members 3 years to < 12 years of age with body weight < 20 kg: glecaprevir 150 mg and pibrentasvir 60 mg per day;
   c. Pediatric members 3 years to < 12 years of age with body weight 20 kg to < 30 kg: glecaprevir 200 mg and pibrentasvir 80 mg per day;
   d. Pediatric members 3 years to < 12 years of age with body weight 30 kg to < 45 kg: glecaprevir 250 mg and pibrentasvir 100 mg 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.CPA.09 for commercial.

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 – CP.CPA.09 for commercial or evidence of coverage documents;
B. Treatment-experienced patients with both NS3/4A protease inhibitor AND NS5A inhibitor, such as combination therapies including: Technivie, Viekira, and Zepatier.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AASLD: American Association for the Study of Liver Diseases
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

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®)	**Genotypes 1 through 6** Without cirrhosis or with compensated cirrhosis, treatment naïve or NS3/4A protease inhibitor +/- pegIFN/ RBV-experienced: One tablet PO QD for 12 weeks	sofosbuvir 400 mg/ velpatasvir 100 mg (1 tablet) per day
sofosbuvir/velpatasvir (Epclusa®)	**Genotypes 1 through 6** Treatment-naïve and treatment-experienced patients, post-liver transplant with compensated cirrhosis or without cirrhosis: One tablet PO QD for 12 weeks	sofosbuvir 400 mg/ velpatasvir 100 mg (1 tablet) per day
Vosevi® (sofosbuvir/ velpatasvir/ voxilaprevir)	**Genotype 1-6** Treatment-experienced with NS5A inhibitor* with or without compensated cirrhosis: One tablet PO QD for 12 weeks	One tablet (sofosbuvir 400 mg/ velpatasvir 100 mg/ voxilaprevir 100 mg) per day
Vosevi® (sofosbuvir/ velpatasvir/ voxilaprevir)	**Genotype 1a or 3** Treatment-experienced with a sofosbuvir-containing regimen without NS5A inhibitor* with or without compensated cirrhosis: One tablet PO QD for 12 weeks	One tablet (sofosbuvir 400 mg/ velpatasvir 100 mg/ voxilaprevir 100 mg) per day
Vosevi® (sofosbuvir/ velpatasvir/ voxilaprevir)	**Genotype 1-6** Treatment-experienced with Vosevi with or without compensated cirrhosis: Vosevi one tablet PO QD with weight-based RBV for 24 weeks‡	One tablet (sofosbuvir 400 mg/ velpatasvir 100 mg/ voxilaprevir 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.
Treatment-experienced refers to previous treatment with NS3 protease inhibitor (telaprevir, boceprevir, or simeprevir) and/or peginterferon/RBV unless otherwise stated.
** See Appendix D*
‡ Off-label, AASLD-IDSA guideline-supported dosing regimen

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s):
  - Patients with severe hepatic impairment (Child-Pugh B or C)

- Co-administration with atazanavir or rifampin
- 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
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

- Acceptable medical justification for inability to use Epclusa (preferred product):
  - In patients indicated for co-administration of Epclusa with ribavirin: contraindications to ribavirin
- Unacceptable medical justification for inability to use Epclusa (preferred product):
  - Coadministration with omeprazole up to 20 mg is not considered an acceptable medical justification for inability to use for 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 Vosevi (preferred product):
  - In patients indicated for co-administration with amiodarone: serious symptomatic bradycardia in patients taking amiodarone, with cardiac monitoring recommended.
- 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.
- Due to higher rates of virologic failure and treatment-emergent drug resistance, the data do not support labeling for treatment of HCV genotype 1 infected patients who are both NS3/4A PI and NS5A inhibitor-experienced.
- Child-Pugh Score:

	1 Point	2 Points	3 Points
Bilirubin	Less than 2 mg/dL	2-3 mg/dL	Over 3 mg/dL

	1 Point	2 Points	3 Points
	Less than 34 umol/L	34-50 umol/L	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

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
Genotypes 1-6: Treatment-naive	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; Peds age 3 years to < 12 years of age with body weight < 20 kg: glecaprevir 150 mg/pibrentasvir 60 mg per day;	FDA-approved labeling
Genotypes 1, 2, 4, 5, or 6: 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		
Genotype 3: Treatment-experienced with IFN/pegIFN, RBV and/or sofosbuvir	Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks		

Indication	Dosing Regimen	Maximum Dose	Reference
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; 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	
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		
Genotype 1-6: Treatment-naïve or treatment-experienced, post-liver or kidney transplantation without cirrhosis or with compensated cirrhosis	Three tablets PO QD for 12 weeks (A 16-week treatment duration is recommended in genotype 1-infected patients who are NS5A inhibitor* experienced without prior treatment with an NS3/4A protease inhibitor† or in genotype 3-infected patients who are IFN/pegIFN, RBV and/or sofosbuvir treatment-experienced)		
Genotypes 1-6: Patients with prior sofosbuvir/velpatasvir/ voxilaprevir treatment failure	With or without compensated cirrhosis: Mavyret 3 tablets PO QD + Sovaldi 400 mg + weight-based RBV for 16 weeks	Three tablets (glecaprevir 300 mg/pibrentasvir 120 mg) per day	AASLD-IDSA (updated March 2021)

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.
** In Mavyret clinical trials, subjects were treated with prior regimens containing ledipasvir and sofosbuvir or daclatasvir with (peg)interferon and ribavirin*
† In Mavyret clinical trials, subjects were treated with prior regimens containing simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with (peg)interferon and ribavirin.

VI. Product Availability

- Tablet: glecaprevir 100 mg and pibrentasvir 40 mg
- Oral pellet: glecaprevir 50 mg and pibrentasvir 20 mg

VII. References

1. Mavyret Prescribing Information. North Chicago, IL: AbbVie Inc.; June 2021. Available at: www.mavyret.com. Accessed July 9, 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. CDC. Hepatitis C Q&As for health professionals. Last updated August 7, 2020. Available at: https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm. Accessed April 15, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created. Safety criteria were 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.	08.15.17	08.17
Initial approval criteria was clarified from "up to a total of 16 weeks" to "8 to up to a total of 16 weeks" per Corporate P&T feedback.	09.05.17	11.17
3Q 2018 annual review: removed requirement for HBV verification; added requirement that prescribed regimen should be consistent with FDA or AASLD recommendations; added specific examples of extrahepatic manifestations in appendix G; expanded duration of tx required for COC from 30 days 40 days; repeated in initial and continued approval criteria the requirement against treatment-experience with both NS3/4A protease inhibitor AND NS5A inhibitors, as previously only listed in section III. diagnoses/ indications NOT allowed; references reviewed and updated.	05.22.18	08.18
Removed requirement for advanced fibrosis or other candidacy for therapy following approved clinical guidance; combined with and retired CP.CPA.EX.285 for HNAZ exchange lines of business.	09.03.18	
No clinically significant changes: modifications made to update template.	01.07.19	
3Q 2019 annual review: updated age ≥ 12 or weight ≥ 45 kg to be consistent with updated FDA approved indication; references reviewed and updated.	05.01.19	08.19
Via CP.PCH.18: CP.CPA.285 retired and combined with HIM to CP.PCH.18; added requirement that life expectancy ≥ 12 months with HCV treatment and participation in a medication adherence program; added new prescriber requirement to include a "provider who has expertise in treating HCV based on a certified training program"; Appendix F (Healthcare Provider HCV Training) added. RT4: updated dosing recommendations to 8 weeks total duration of therapy for treatment naive HCV with compensated cirrhosis across all genotypes (1-6).	12.03.19	02.20
3Q 2020 annual review: CP.PCH.18 retired and CP.CPA.285 unretired per June SDC and prior clinical guidance; allowed use in combination with Sovaldi after Vosevi failure; references reviewed and updated.	06.10.20	08.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Per September SDC and prior clinical guidance for 1/1/21 effective, added redirection to brand Epclusa or Vosevi.	09.22.20	
3Q 2021 annual review: no significant changes; added clarification that redirection to Eplcusa is for brand Epclusa in criteria; included reference to Appendix E with addition of contraindications that would warrant bypassing preferred agents; updated Appendix B therapeutic alternatives and section V dosing tables; RT4: updated criteria for Mavyret pediatric age expansion to 3 years and older along with pediatric dosing and new oral pellet dosage formulation; references reviewed and updated.	07.12.21	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. 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.

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