Clinical Policy: Glecaprevir/Pibrentasvir (Mavyret)

Reference Number: GA.PMN.24
Effective Date: 9/17
Last Review Date: 7/2024 Revision Log
Line of Business: Medicaid

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
It is the policy of health plans affiliated with Centene Corporation® that Mavyret is **medically necessary** when the following criteria are met:

I. Approval Criteria
*** Provider must submit documentation (including office chart notes and lab results) supporting that member has met all approval criteria ***

A. Hepatitis C Infection (must meet all)**:**
1. Diagnosis of chronic HCV infection as evidenced by detectable serum HCV RNA (ribonucleic acid) levels by quantitative assay in the last 6 months;
2. Member meets one of the following (a or b):
   a. Member is treatment-naïve and has either compensated cirrhosis or no cirrhosis (i.e., eligible for simplified treatment regimen);
   b. Confirmed HCV genotype is one of the following (i, ii, iii, or iv):*
      i. For treatment-naïve members: genotypes 1, 2, 3, 4, 5, or 6;
      ii. For members treatment-experienced with interferon (IFN)/pegylated-interferon (pegIFN), ribavirin (RBV), and/or sofosbuvir only: genotypes 1, 2, 3, 4, 5, or 6;
      iii. For members treatment-experienced with either an NS5A inhibitor or an NS3/4A protease inhibitor: genotype 1 (*see Appendix D*);

iv. For Vosevi®- or Mavyret-experienced members: genotype 1, 2, 3, 4, 5, or 6;
**Chart note documentation and copies of lab results are required*

3. Age ≥ 3 years:
4. Documentation of the treatment status of the patient (treatment-naïve or treatment-experienced);
5. Documentation of cirrhosis status of the patient (no cirrhosis, compensated cirrhosis, or decompensated cirrhosis);
6. Life expectancy ≥ 12 months with HCV treatment;
7. Member is not treatment-experienced with both NS3/4A protease inhibitor AND NS5A inhibitors, such as combination therapies including Technivie ™, Viekira ™, and Zepatier ®;
8. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see Section IV Dosage and Administration for reference*);
9. If cirrhosis is present, confirmation of Child-Pugh A status;
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. 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 IV Dosages 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.

II. 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;

B. HCV in treatment-experienced members with both NS3/4A protease inhibitor AND NS5A inhibitor, such as combination therapies including: Technivie, Viekira, and Zepatier.

III. Appendices/General Information

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

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindications
  - Patients with moderate or 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
Daklinza	Daclatasvir				

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	
Olysio‡				Simeprevir	
Sovaldi		Sofosbuvir			
Technivie*‡	Ombitasvir			Paritaprevir	Ritonavir
Viekira /PAK*	Ombitasvir		Dasabuvir	Paritaprevir	Ritonavir
Vosevi*	Velpatasvir	Sofosbuvir		Voxilaprevir	
Zepatier*	Elbasvir			Grazoprevir	

*Combination drugs

‡ *Olysio and Technivie are no longer commercially available.*

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.
- 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 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

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.

IV. 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	FDA-approved labeling

Indication	Dosing Regimen	Maximum Dose	Reference
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	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; 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 3: Treatment-experienced with IFN/pegIFN, RBV and/or sofosbuvir	Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks		
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		
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 or glecaprevir/pibrentasvir 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 October 2022)

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.
** See appendix D*
ǂ PRS: prior treatment experience with regimens containing IFN/pegIFN, RBV, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor

V. Product Availability

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

References

1. Mavyret Prescribing Information. North Chicago, IL: AbbVie Inc.;October 2023. Available at: https://www.rxabbvie.com/pdf/mavyret_pi.pdf. Accessed May 7, 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	Approval Date
Policy created	09/17	9/17
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. Removed background sections. Updated general information and contraindication section to be consistent with corporate HCV policies.	2/21/19	2/19
Annual review. Updated age ≥ 12 or weight ≥ 45 kg to be consistent with updated FDA approved indication. Added missing criterion for requirement against treatment-experience with both NS3/4A protease inhibitor AND NS5A inhibitors.	10/19	10/19
RT4: updated dosing recommendations to 8 weeks total duration of therapy for treatment naive HCV with compensated cirrhosis across all genotypes (1-6).Removed Appendix C for Metavir scoring. Removed Mayvret acceptable/unacceptable medical justification and added statement regarding labeling of HCV genotype 1 infected patients in Appendix E. Updated order of all other Appendices. Updated references.	4/2020	4/2020
Added Mavyret + Sovaldi + RBV preference for Vosevi treatment failures per preferencing and per updated AASLD/IDSA HCV guideline; references reviewed and updated.	7/2020	7/2020
Annual review. Added information on drug inclusions for clinical trials in the FDA Approved Indications section. Added moderate hepatic impairment and boxed warning for hepatitis B reactivation to Appendix C: Contraindication. Added a statement regardinig Olysio and Technivie no	4/2021	4/2021

Reviews, Revisions, and Approvals	Date	Approval Date
longer being commercially available to Appendix D. Changed Centene Logo to PSHP Logo. Made minor formatting and typo changes. References reviewed.		
Updated Section III table with FDA and AASLD recommended regimens; references reviewed and updated.	7/2021	7/2021
Updated Section V table with FDA and AASLD recommended regimens; RT4: updated criteria for Mavyret pediatric age expansion to 3 years and older along with pediatric dosing and new oral pellet dosage formulation; Added a Diagnoses/Indications for which coverage is NOT authorized section to be consistent with corporate. Made minor formatting changes. References reviewed and updated.	1/2022	1/2022
3Q 2022 annual review. Clarified confirmed genotype criterion 2 by removing "in combination with sofosbuvir" from Vosevi-experienced members to align with preceding bullets which include genotype and previous treatment experience (approved regimens are listed in section V); references reviewed and updated.	7/2022	7/2022
Template changes applied to other diagnoses/indications section.	1/2023	1/2023
3Q 2023 annual review: added a bypass for HCV genotype documentation if member is treatment-naïve and has either compensated cirrhosis or no cirrhosis (i.e., eligible for AASLD-IDSA simplified treatment regimen); added previous Mavyret experience to initial approval criteria scenarios per AASLD recommended regimens; references reviewed and updated.	7/2023	7/2023
3Q 2024 annual review: removed qualifier of "chronic" from HCV criteria as AASLD-IDSA recommends treatment of both acute and chronic HCV; added Appendix F for guidance on incomplete adherence and AASLD-IDSA recommended management of treatment interruptions; references reviewed and updated.	7/2024	7/2024

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.