Clinical Policy: Glecaprevir/Pibrentasvir (Mavyret)

Reference Number: LA.PHAR.348
Effective Date: 09/17
Last Review Date: 07/18 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

Mavyret is indicated for the treatment of:

- Patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection*** without cirrhosis and with compensated cirrhosis (Child-Pugh A)
- Adult patients with 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.
*** In clinical trials, prior treatment experience included regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A protease inhibitor or NS5A inhibitor.

Policy/Criteria

Provider must submit documentation (which may include 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® 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 HCV RNA (ribonucleic acid) levels in the last 6 months;
2. Confirmed HCV genotype is one of the following (a, b, or c);
   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;
   a. For patients treatment-experienced with either an NS5A inhibitor or an NS3/4A protease inhibitor: genotype 1 (*see Appendix E*);
   **Chart note documentation and copies of lab results are required*
3. Age ≥ 18 years;
4. If cirrhosis is present, confirmation of Child-Pugh A status;

5. Life expectancy ≥ 12 months with HCV treatment;
6. Documentation required that member is not actively participating in alcohol and/or illicit IV drugs use, if applicable;
7. Advanced liver disease defined as a or b:
   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);
      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.
8. Member is not treatment-experienced with both NS3/4A protease inhibitor AND NS5A inhibitors, such as combination therapies including Technivie, Viekira, and Zepatier;
9. Member agrees to participate in a medication adherence program including both of the following components:
   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 glecaprevir 300 mg and pibrentasvir 120 mg (3 tablets) 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.

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, or 3);
      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*);
2. Member is responding positively to therapy;
3. Dose does not exceed glecaprevir 300 mg and pibrentasvir 120 mg (3 tablets) 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.

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;
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
APRI: AST to platelet ratio
FDA: Food and Drug Administration
FIB-4: Fibrosis-4 index
HBV: hepatitis B virus
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
HIV: human immunodeficiency virus
IDSA: Infectious Diseases Society of America
IQR: interquartile range
MRE: magnetic resonance elastography
NS3/4A, NS5A/B: nonstructural protein
PegIFN: pegylated interferon
RBV: ribavirin
RNA: ribonucleic acid

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications

- Patients with severe hepatic impairment (Child-Pugh C)
- Co-administration with atazanavir or rifampin

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	
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.

- 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

- Mavyret is FDA-approved for the treatment of patients with genotypes 1, 2, 3, 4, 5, or 6 in:
  - Treatment-naive patients
  - Patients treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose	Reference
Genotypes 1-6: Treatment-naive	Without cirrhosis: Three tablets PO QD for 8 weeks With compensated cirrhosis: Three tablets PO QD for 12 weeks	Three tablets (glecaprevir 300 mg/pibrentasvir 120 mg) per day	1) FDA-approved labeling 2) AASLD-IDSA (updated September 2017)
Genotypes 1, 2, 4, 5, or 6: Treatment-experienced with IFN/pegIFN + RBV	Without cirrhosis: Three tablets PO QD for 8 weeks With compensated cirrhosis: Three tablets PO QD for 12 weeks	Three tablets (glecaprevir 300 mg/pibrentasvir 120 mg) per day	1) FDA-approved labeling 2) AASLD-IDSA (updated September 2017)
Genotypes 1 or 2**:** Treatment-experienced with sofosbuvir	Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 12 weeks	Three tablets (glecaprevir 300 mg/pibrentasvir 120 mg) per day	1) FDA-approved labeling 2) AASLD-IDSA (updated September 2017)

Indication	Dosing Regimen	Maximum Dose	Reference
Genotypes 3, 4, 5, or 6: Treatment-experienced with sofosbuvir	Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 12 weeks	Three tablets (glecaprevir 300 mg/ pibrentasvir 120 mg) per day	FDA-approved labeling
Genotype 3: Treatment-experienced with IFN/pegIFN + RBV	Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks	Three tablets (glecaprevir 300 mg/pibrentasvir 120 mg) per day	1) FDA-approved labeling 2) AASLD-IDSA (updated September 2017)
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	Three tablets (glecaprevir 300 mg/pibrentasvir 120 mg) per day	1) FDA-approved labeling 2) AASLD-IDSA (updated September 2017)
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	Three tablets (glecaprevir 300 mg/pibrentasvir 120 mg) per day	1) FDA-approved labeling 2) AASLD-IDSA (updated September 2017)
Genotype 1-6: Treatment-naïve or treatment-experienced, post-liver transplantation‡ with or without compensated cirrhosis	Three tablets PO QD for 12 weeks	Three tablets (glecaprevir 300 mg/pibrentasvir 120 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.
‡ *Off-label, AASLD-IDSA guideline-supported dosing regimen*
** See appendix E*

VI. Product Availability

Tablets: glecaprevir 100 mg and pibrentasvir 40 mg

VII. References

1. Mavyret Prescribing Information. North Chicago, IL: AbbVie Inc.; December 2017. Available at: www.mavyret.com. Accessed May 21, 2018.
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 September 21, 2017. Available at: https://www.hcvguidelines.org/. Accessed May 1, 2018.

3. Platt L, Easterbrook P, Gower E, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lanet Infect Dis 2016;16:797-808. http://dx.doi.org/10.1016/
4. Centers for Disease Control and Prevention. HIV and viral hepatitis: fact sheet. June 2016. Available at: https://www.cdc.gov/hiv/pdf/library/factsheets/hiv-viral-hepatitis.pdf. Accessed March 13, 2018.
5. Bonder A, Afdhal N. Utilization of FibroScan in clinical practice. Curr Gastroenterol Rep. 2014; 16(372): 1-7. DOI 10.1007/s11894-014-0372-6.
6. Halfon P, Bourliere M, Deydier R, et al. Independent prospective multicenter validation of biochemical markers (Fibrotest–Actitest) for the prediction of liver fibrosis and activity in patients with chronic hepatitis C: The Fibropaca study. Am J Gastroenterol. 2006; 101: 547-555. DOI: 10.1111/j.1572-0241.2006.0411.x
7. Hepatitis C Virus (HCV) FibroSure. Laboratory Corporation of America Holdings and Lexi-Comp, Inc. Available at https://www.labcorp.com. 2016. Accessed May 1, 2018.
8. Hepatitis C Virus (HCV) FibroTest-ActiTest Panel. Nichols Institute/Quest Diagnostics. Available at http://education.questdiagnostics.com/physician_landing_page. 2017. Accessed May 1, 2018.
9. Hepatitis C Virus (HCV) FIBROSpect II. Prometheus Therapeutics and Diagnostics. Available at http://www.prometheuslabs.com/Resources/Fibrospect/Fibrospect_II_Product_Detail_Sheet_FIB16005_04-16.pdf. April 2016. Accessed May 1, 2018.
10. Hsieh YY, Tung SY, Lee K, et al. Routine blood tests to predict liver fibrosis in chronic hepatitis C. World J Gastroenterol. February 28, 2012; 18(8): 746-53. doi: 10.3748/wjg.v18.i8.746.

Reviews, Revisions, and Approvals	Date	Approval Date
Policy created.	08/17	09/17
Due to State requirements, removed prescriber restrictions regarding who can prescribe Hepatitis C DAA agents; 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,; Added statement that NO Fibrosis score is required for HIV/HCV co-infected members Changed language to one serologic test OR one radiologic test from one serologic test and one radiologic test	03/18	05/18
3Q 2018 annual review: removed requirement for HBV verification; expanded duration of tx required for COC from 30 days to 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.	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.

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.