Clinical Policy: Glecaprevir/Pibrentasvir (Mavyret)

Reference Number: HIM.PA.SP36
Effective Date: 08.01.17
Last Review Date: 06.18
Line of Business: HIM

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:

- 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.

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, or c);
   1) For treatment-naïve patients: genotypes 1, 2, 3, 4, 5, or 6;
   2) For patients treatment-experienced with interferon (IFN)/pegylated-interferon (pegIFN), ribavirin (RBV), and/or sofosbuvir only: genotypes 1, 2, 3, 4, 5, or 6;
   3) 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. Prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious disease specialist;
4. Age ≥ 18 years;
5. If cirrhosis is present, confirmation of Child-Pugh A status;
6. If contraindicated to Mavyret, member must use Epclusa® for applicable genotypes and treatment status (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced;
7. Life expectancy ≥ 12 months with HCV treatment;

8. Documented sobriety from alcohol and illicit IV drugs for ≥ 6 months prior to starting therapy, if applicable;
9. Member is not treatment-experienced with both NS3/4A protease inhibitor AND NS5A inhibitors, such as combination therapies including Technivie™, Viekira™, and Zepatier®;
10. Member agrees to participate in a medication adherence program including both of the following components (a and b):
    1) Medication adherence monitored by pharmacy claims data or member report;
    2) Member's risk for non-adherence identified by adherence program or member/prescribing physician follow-up at least every 4 weeks;
11. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see Section V for reference*);
12. Dose does not exceed glecaprevir 300 mg and pibrentasvir 120 mg per day (3 tablets/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): HIM.PHAR.21 for health insurance marketplace.

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 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 glecaprevir 300 mg and pibrentasvir 120 mg per day (3 tablets/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): HIM.PHAR.21 for health insurance marketplace.

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 – HIM.PHAR.21 or evidence of coverage documents;

B. HCV in treatment-experienced patients with both NS3/4A protease inhibitor AND NS5A inhibitors, 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
Epclusa® (sofosbuvir/ velpatasvir)	Without cirrhosis or with compensated cirrhosis, treatment-naïve or pegIFN/ RBV-experienced patient: **Genotype 1-6** One tablet PO QD for 12 weeks (GT 3 with compensated cirrhosis for pegIFN/RBV-experienced patient may use: one tablet PO QD with weight-based RBV for 12 weeks) ǂ	Epclusa: sofosbuvir 400 mg /velpatasvir 100 mg (1 tablet) per day
Epclusa® (sofosbuvir/ velpatasvir)	With decompensated cirrhosis treatment-naïve or treatment-experienced* patient: **Genotype 1-6** One tablet PO QD with weight-based RBV for 12 weeks	Epclusa: sofosbuvir 400 mg /velpatasvir 100 mg (1 tablet) per day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	(GT 1, 4, 5, or 6 with decompensated cirrhosis and RBV-ineligible may use: one tablet PO QD for 24 weeks) ǂ	
Epclusa® (sofosbuvir/ velpatasvir)	With decompensated cirrhosis in whom prior sofosbuvir- or NS5A-based treatment experienced failed: **Genotype 1-6** One tablet PO QD with weight-based RBV for 24 weeks	Epclusa: sofosbuvir 400 mg /velpatasvir 100 mg (1 tablet) per day
Epclusa® (sofosbuvir/ velpatasvir)	With compensated cirrhosis or without cirrhosis and non-NS5A inhibitor, sofosbuvir-containing regimen-experienced: **Genotype 1b** One tablet PO QD for 12 weeks	Epclusa: sofosbuvir 400 mg /velpatasvir 100 mg (1 tablet) per day
Epclusa® (sofosbuvir/ velpatasvir)	With or without compensated cirrhosis, sofosbuvir + RBV-experienced: **Genotype 2** One tablet PO QD for 12 weeks	Epclusa: sofosbuvir 400 mg /velpatasvir 100 mg (1 tablet) per day
Epclusa® (sofosbuvir/ velpatasvir)	Treatment-naïve and treatment-experienced patients, post-liver transplant with compensated cirrhosis or decompensated cirrhosis: **Genotype 2 or 3** One tablet PO QD with weight-based RBV for 12 weeks	Epclusa: sofosbuvir 400 mg /velpatasvir 100 mg (1 tablet) per day
Epclusa® (sofosbuvir/ velpatasvir)	Treatment-naïve with cirrhosis or treatment-experienced* patient: **Genotype 3 with NS5A Y93H polymorphism** One tablet PO QD with weight-based RBV for 12 weeks	Epclusa: sofosbuvir 400 mg /velpatasvir 100 mg (1 tablet) 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

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

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			
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 E: 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

	1 Point	2 Points	3 Points
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

- The World Health Organization (WHO) estimates that at the global level, there are approximately 2,278,400 HIV-HCV co-infections (IQR 1,271,300 to 4,417,000) of which 1,362,700 (IQR 847,770 to 1,381,800) in people who inject drugs (PWID), equaling an overall co-infection prevalence in HIV-infected individuals of **6.2%** (IQR 3.4 to 1.9). In North America specifically, the meta-analysis showed that the best estimate for the percentage of total HIV-infected individuals with HCV co-infection was about **14%.** On the other hand, the Centers of Disease Control and Prevention (CDC) estimates that about **25%** of people with HIV in the US are co-infected with HCV.
  - As of March 2018, there are a total of 1.38 million members enrolled in Centene Health Insurance Marketplace. Out of those members, about 6,300 members are estimated to be diagnosed with HIV based on claims data, with about 173 members with recent claims for atazanavir and/or efavirenz. And based on the CDC as well as WHO prevalence estimation for North America, we can predict that about 14% to 25%, or 882 to 1,575 members, with HIV infection may be co-infected with HCV, with about 25 to 44 members who may not be eligible for treatment with Mavyret due to drug interactions involving atazanvir and/or efavirenz.

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)
Genotypes 3, 4, 5, or 6:	Without cirrhosis or with compensated cirrhosis:	Three tablets (glecaprevir 300 mg/	FDA-approved labeling

Indication	Dosing Regimen	Maximum Dose	Reference
Treatment-experienced with sofosbuvir	Three tablets PO QD for 12 weeks	pibrentasvir 120 mg) per day	
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 1, 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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created. 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.	08.15.17	08.17
Requirement for Hep B screening was not yet approved by P & T and it was therefore removed as this is under the purview of the specialist	09.14.17	11.19
3Q18 annual review: 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; expanded duration of tx required for COC from 30 days to 40 days; required verification of genotype for COC; removed requirement for advanced liver disease; references reviewed and updated.	05.22.18	06.18
No significant change: added financial redirection to Epclusa if contraindicated to Mavyret.	07.13.18	

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 Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.