Clinical Policy: Glecaprevir/Pibrentasvir (Mavyret)

Reference Number: ERX.SPA.215
Effective Date: 08.15.17
Last Review Date: 08.21
Line of Business: Commercial, Medicaid

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

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** 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 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 members: genotypes 1, 2, 3, 4, 5, or 6;
   b. For members treatment-experienced with interferon (IFN)/pegylated-interferon (pegIFN), ribavirin (RBV), and/or sofosbuvir only: genotypes 1, 2, 3, 4, 5, or 6;
   c. For members treatment-experienced with either an NS5A inhibitor or an NS3/4A protease inhibitor: genotype 1 (*see Appendix D*);
   d. For Vosevi-experienced members, member meets both of the following (i and ii):
      i. Member has genotype 1, 2, 3, 4, 5, or 6;
      ii. Member must use Vosevi in combination with weight-based RBV, unless contraindicated or clinically significant adverse effects are experienced;

   **Chart note documentation and copies of lab results are required*
3. Prescribed by or in consultation with a gastroenterologist, hepatologist, or 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 has contraindication(s) or clinically significant adverse effects to Harvoni®, Epclusa®, and Vosevi® (*see Appendix E*);
7. Life expectancy ≥ 12 months with HCV treatment;
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. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see Section V Dosage and Administration for reference)*;
10. 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 ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
    b. 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 D*);
            4) For Vosevi-experienced members: genotypes 1, 2, 3, 4, 5, or 6;
2. Member is responding positively to therapy;
3. 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 ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – ERX.PA.01 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
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 and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Harvoni® (ledipasvir/sofosbuvir)	**Genotype 1** Treatment-naïve without cirrhosis, who are HIV-uninfected, AND whose HCV viral load is less than 6 million IU/mL: One tablet PO QD for 8 weeks* Treatment-naïve without cirrhosis (not meeting the 8 week treatment indication requirements above) or with compensated cirrhosis: One tablet PO QD for 12 weeks **Genotype 4, 5, 6** Treatment naïve and treatment-experienced, without cirrhosis or with compensated cirrhosis: One tablet PO QD for 12 weeks	1 tablet/day
Epclusa® (sofosbuvir/velpatasvir)	**Genotype 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	1 tablet/day
Epclusa® (sofosbuvir/ velpatasvir) plus RBV	**Genotype 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	1 tablet/day
Vosevi® (sofosbuvir/velpatasvir/ voxilaprevir)	**Genotypes 1 through 6** Without cirrhosis or with compensated cirrhosis, treatment in patients previously treated with an HCV regimen containing an NS5A inhibitor: One tablet PO QD for 12 weeks **Genotypes 1a or 3** Without cirrhosis or with compensated cirrhosis, treatment in patients previously treated with an HCV	1 tablet/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	regimen containing sofosbuvir without an NS5A inhibitor: One tablet PO QD for 12 weeks	
Vosevi® (sofosbuvir/velpatasvir/ voxilaprevir) + RBV	**Genotypes 1 through 6*** Without cirrhosis or with compensated cirrhosis, treatment in patients previously treated Vosevi: One tablet PO QD for 24 weeks*	Varies

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.
**Off-label regimen recommended by AASLD/IDSA HCV guideline, updated March 2021*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Patients with severe hepatic impairment (Child-Pugh B or C)
  - Co-administration with atazanavir and rifampin
- Boxed warning(s): risk of hepatitis B virus reactivation in patients coinfected with HCV and HBV.

Appendix D: Direct-Acting Antivirals (DAAs) 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 or Harvoni (preferred products):
  - In patients indicated for co-administration with ribavirin: contraindications to ribavirin
  - In patients indicated for co-administration with amiodarone: serious symptomatic bradycardia in patients taking amiodarone, with cardiac monitoring recommended.
- 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.

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; 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	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		
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		

Indication	Dosing Regimen	Maximum Dose	Reference
	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.
** See appendix D*

VI. Product Availability

- Tablet: glecaprevir 100 mg with 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 12, 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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created. *Safety criteria was applied according to the safety guidance discussed at CPAC and per EPS.PHARM.31. 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
Added redirection to Harvoni, Epclusa, and Vosevi per 2018 formulary status	03.20.18	
3Q 2018 annual review: removed requirement for HBV verification; expanded duration of treatment 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.	05.22.18	08.18
3Q 2019 annual review: removed advanced liver disease requirement to align with 2018 AASLD/IDSA hepatitis C treatment guidelines; updated age ≥ 12 or weight ≥ 45 kg to be consistent with updated FDA approved indication; references reviewed and updated.	05.13.19	08.19
3Q 2020 annual review: added requirement for Vosevi-treatment failures to use Vosevi + RBV per formulary preference and as recommended by AASLD/IDSA HCV guideline; 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; references reviewed and updated.	05.20.20	08.20
3Q 2021 annual review: removed criterion for sobriety documentation as AASLD recommends to treat all patients with HCV except those with short	07.12.21	08.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
life expectancy; 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.		

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.