Clinical Policy: Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi)

Reference Number: GA.PMN.25
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
Sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) is a fixed-dose combination oral tablet. Sofosbuvir is a nucleotide analog HCV NS5B polymerase inhibitor, velpatasvir is an NS5A inhibitor, and voxilaprevir is an NS3/4A protease inhibitor.

FDA Approved Indication(s)
Vosevi is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have:

- Genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor*;
- Genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor**.
    - Additional benefit of Vosevi over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.

Policy/Criteria
It is the policy of health plans affiliated with Centene Corporation® that Vosevi 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 HCV RNA (ribonucleic acid) levels by quantitative assay in the last 6 months;
2. Age ≥ 18 years;
3. Member meets one of the following (a, b, or c):
    a. If HCV genotype 1, 2, 3, 4, 5 or 6, member has previously been treated with an HCV regimen containing one of the following NS5A inhibitors: daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, or velpatasvir;
    b. If HCV genotype is 1a or 3, member has previously been treated with an HCV regimen containing sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir);

c. Member is treatment naïve and i-iii:
   i. HCV genotype is 3;
   ii. Member has compensated cirrhosis;
   iii. Documentation for the presence of baseline NS5A resistance-associated substitution (RAS) Y93H for velpatasvir;

4. For HCV treatment-experienced member: Member has received ≥ 8 weeks of the prior direct-acting antiviral agent (DAA) regimen from 3a or 3b above, unless virologic failure was determined prior to 8 weeks of therapy;
5. Member must use **Mavyret®** or **sofosbuvir/velpatasvir (Epclusa® *authorized generic*)** as indicated below if member meets one of the following (a, b, c, or d), unless contraindicated or clinically significant adverse effects are experienced:
   a. For HCV genotype 1 and previous treatment with an HCV regimen containing an NS5A inhibitor without an NS3/4A protease inhibitor (i.e., Daklinza®, Epclusa®, Harvoni®): Member must use Mavyret;
   b. For HCV genotype 1a or 3 previous treatment with with an HCV regimen containing sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir): Member must use Mavyret;
   c. For HCV genotype 1 through 6 and previous treatment with Vosevi: Mavyret must be used in combination with Sovaldi® and RBV;
   d. For HCV genotype 3, treatment-naive, compensated cirrhosis with documentation of the presence of baseline NS5A RAS Y93H for velpatasvir: Member must use Epclusa (*authorized generic preferred*) in combination with RBV or Mavyret;
6. Life expectancy ≥ 12 months with HCV treatment;
7. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see Appendix D Dosage*);
8. 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*);
9. Prescribed dose does not exceed one tablet (sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg) daily.

Approval duration: up to a total of 24 weeks*
*(*Approved duration should be consistent with a regimen in Appendix D FDA approved dosages and Treatment Duration)*

B. Other diagnoses/indications (must meet all)**:**

1. Member must use **Mavyret®** or **sofosbuvir/velpatasvir (Epclusa® *authorized generic*),** if applicable for the requested indication, unless clinically significant adverse effects are experienced or both are contraindicated;
2. Must meet one of the following (a or b):
   a. 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 (i or ii):

i. 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
ii. 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

b. 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. 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

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
Mavyret® (glecaprevir/ pibrentasvir)	Treatment-experienced with IFN/pegIFN, RBV and/or sofosbuvir: **Genotypes 1, 2, 4, 5, or 6** Without cirrhosis: Three tablets PO QD for 8 weeks With compensated cirrhosis: Three tablets PO QD for 12 weeks	Mavyret: glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day
Mavyret® (glecaprevir /pibrentasvir)	Treatment-experienced with IFN/pegIFN, RBV and/or sofosbuvir: **Genotype 3**	Mavyret: glecaprevir 300 mg/ pibrentasvir

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks	120 mg (3 tablets) per day
Mavyret® (glecaprevir /pibrentasvir)	Treatment-experienced with NS5A inhibitor without prior NS3/4A protease inhibitor: **Genotype 1** Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 16 weeks	Mavyret: glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day
Mavyret® (glecaprevir /pibrentasvir)	Treatment-experienced with NS3/4A protease inhibitor without prior NS5A inhibitor: **Genotype 1** Without cirrhosis or with compensated cirrhosis: Three tablets PO QD for 12 weeks	Mavyret: glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day
Mavyret® (glecaprevir /pibrentasvir)	Treatment-naive: **Genotype 3** With compensated cirrhosis: Three tablets PO QD for 8 weeks	Mavyret: glecaprevir 300 mg/ pibrentasvir 120 mg (3 tablets) per day
sofosbuvir/ velpatasvir (Epclusa®) + RBV	Treatment-naive: **Genotype 3** With compensated cirrhosis and baseline NS5A RAS Y93H: sofosbuvir/velpatasvir 400 mg/100 mg + weight-based RBV for 12 weeks	sofosbuvir 400 mg /velpatasvir 100 mg (one tablet) per day
Mavyret®(glecaprevir /pibrentasvir) + Sovaldi® (sofosbuvir) + RBV	With prior sofosbuvir/velpatasvir/ voxilaprevir or prior glecaprevir/pibrentasvir treatment failure, with compensated cirrhosis or without cirrhosis **Genotypes 1-6**ǂ: Sovaldi 400 mg + Mavyret 300 mg/120 mg + weight-based RBV for 16 weeks	Varies

Theraputic alternatives are listed as Brand Name® (generic) when the drug is a available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

ǂ *Off-label, AASLD-IDSA guideline-supported dosing regimen*

Appendix C: Contraindications

- Coadministration with 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				
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

- 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.

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 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.

III. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose	Reference
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	1) FDA-approved labeling 2) AASLD-IDSA (updated November 2019)
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		1) FDA-approved labeling 2) AASLD-IDSA (updated November 2019)
Genotype 1-6: Treatment-experienced with Vosevi® with or without compensated cirrhosis	Vosevi one tablet PO QD with weight-based RBV for 24 weeks		AASLD-IDSA (updated November 2019)

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 E*

IV. Product Availability

Tablet: sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg

V. References

1. Vosevi Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; November 2019. Available at: www.vosevi.com. Accessed May 8, 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.
3. Bourliere M, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. NEJM 2017;376:2134-46.

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. Added new preferred treatment tables that includes dosage and frequency based on genotype for Mavyret. Removed background sections. Updated general information and contraindication section to be consistent with corporate HCV policies.	2/21/19	2/19
Annual review. Updated wording of approval criteria for meeting use of preferential Mavyret.	10/19	10/19
Added Epclusa to Appendix B. Removed Appendix D for Metavir scoring. Removed dosing for Mavyret treatment-naïve. Updated order of all other Appendices. Updated references.	4/2020	4/2020
Added preferred re-direction for off-label Mavyret + Sovaldi + RBV after Vosevi failure; modified initial and continued approval durations up to 24 weeks to allow for post Vosevi failure off-label indication dosing per per AASLD/IDSA guideline; references reviewed and updated.	7/2020	7/2020

Reviews, Revisions, and Approvals	Date	Approval Date
Annual review. Added "quantity assay" specifically for testing to initial criteria. Added that preferred Mavyret needs to be used as a single agent or in combination as indicated to initial criteria. Updated criteria to include pibrentasvir as an acceptable option for previous treatment with an HCV regimen containing an NS5A inhibitor to align with appendix D table; references reviewed and updated.Added additional Mayvret plus RBV dosing regimen to Therapeutic Alternatives table. Removed "chronic HCV infection" verbiage from Therapeutic Alternative table to be consistent with CNC policy. Added Box Warning for hepatitis B reactivation to Appendix C: Contraindications. Added Mayvret and Vosevi to Appendix D-Direct Acting Antivirals for Treatment of HCV infection and removed Olysio, Technivie, and Viekira XR as these were previously removed from the market. Changed Centene Logo to PSHP Logo. Minor formatting changes throughout document. References reviewed.	4/2021	4/2021
Updated Appendix B therapeutic alternatives; removed the appendix E acceptable medical justification section for inability to use Mavyret as it overlaps with Vosevi clinical parameters for not using; references reviewed and updated.	7/2021	7/2021
3Q 2022 annual review. Removed Appendix E unacceptable medical justification section for inability to use Mavyret as it overlaps with Vosevi warnings, removed precaution of concurrent anticoagulation therapy as it is a caution and not an absolute contraindication and removed reference to Appendix E from initial criteria; references reviewed and updated.	7/2022	7/2022
Added pathway to Vosevi approval for a specific treatment-naïve genotype 3 scenario per AASLD guideline with redirection to preferred Mavyret or Epclusa; clarified prior DAA regimen is a criterion for an HCV treatment-experienced member. Template changes applied to other diagnoses/indications.	1/2023	1/2023
3Q 2023 annual review: for criterion requiring preferred redirection of Mavyret, added clinical scenario of previous Mavyret failure per AASLD guidance; 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; removed the word "preferred" from Epclusa authorized generic redirection; 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.