Clinical Policy: Sofosbuvir/Velpatasvir (Epclusa)

Reference Number: GA.PMN.06
Effective Date: 12/16
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 (Epclusa®/™) is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor.

FDA Approved Indication(s)
Epclusa is indicated for the treatment of adult and pediatric patients 3 years of age and older with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection:
- Without cirrhosis or with compensated cirrhosis
- With decompensated cirrhosis for use in combination with ribavirin (RBV)

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

I. Initial 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 hepatitis C virus (HCV) infection as evidenced by detectable HCV ribonucleic acid (RNA) levels in the last 6 months;
2. Age ≥ 3 years;
3. Member must use **authorized generic version of Epclusa,** unless contraindicated or clinically significant adverse effects are experienced;
4. Member meets one of the following (a or b):
   a. Member is treatment-naïve and does not have cirrhosis (i.e., eligible for simplified treatment regimen);
   b. Confirmed HCV genotype is 1, 2, 3, 4, 5 or 6;*
   *Chart note documentation and copies of labs results are required
5. For genotype 3: One of the following (a or b):
   a. Laboratory testing for the presence or absence of NS5A resistance-associated substitution (RAS) Y93H for velpatasvir if member meets one of the following scenarios (i or ii):
      i. Member is treatment-naïve and has cirrhosis;
      ii. Member has had previous HCV treatment and has no cirrhosis;

b. Member does not meet one of the above scenarios in 3a;
6. Documentation of the treatment status of the patient (treatment-naïve or treatment-experienced);
7. Documentation of cirrhosis status of the patient (no cirrhosis, compensated cirrhosis, or decompensated cirrhosis);
8. Life expectancy ≥ 12 months with HCV treatment;
9. Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see Section IV Dosage and Administration for reference)*;
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 B*);
11. If prescribed with ribavirin, member has none of the following contraindications:
    a. Pregnancy or possibility of pregnancy - member or partner;
    b. Hypersensitivity to ribavirin;
    c. Coadministration with didanosine;
    d. Significant/unstable cardiac disease;
    e. Hemoglobinopathy (e.g., thalassemia major, sickle cell anemia);
    f. Hemoglobin < 8.5 g/dL.
12. Dose does not exceed one of the following (a or b):
    a. Adult and pediatric members with body weight ≥ 30 kg: sofosbuvir/velpatasvir 400 mg/100 mg (1 tablet) per day;
    b. Pediatric members 3 years of age and older with body weight < 17 kg: sofosbuvir/velpatasvir 150 mg/37.5 mg per day;
    c. Pediatric members 3 years of age and older with body weight 17 kg to < 30 kg: sofosbuvir/velpatasvir 200 mg/50 mg per day.

Approval duration: up to a total of 24 weeks*
*(*Approved duration should be consistent with a regimen in Section III Dosage and Administration)*

B. Other diagnoses/indications (must meet all)**:**
1. Member must use **authorized generic version of Epclusa**, unless contraindicated or clinically significant adverse effects are experienced;
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. 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.

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: Contraindications/Box Warnings

- Epclusa and RBV combination regimen is contraindicated in patients for whom RBV is contraindicated. Refer to the RBV prescribing information for a list of contraindications for RBV.
- Box warning (s): risk of hepatitis B virus reactivation in patients co-infected with HCV and HBV

Appendix C: 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 D: 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.
- AASLD-IDSA simplified treatment recommendations: In their October 2022 HCV guidance, AASLD-IDSA updated treatment recommendations to recommend two simplified regimens for adults with chronic hepatitis C (*any genotype*) who do not have cirrhosis and have not previously received hepatitis C treatment: either Mavyret x8 weeks or Epclusa x12 weeks. With the advent of pangenotypic HCV treatment regimens, HCV genotyping is no longer required prior to treatment initiation for all individuals. In those with evidence of cirrhosis and/or past unsuccessful HCV treatment, treatment regimens may differ by genotype and thus pretreatment genotyping is recommended. For noncirrhotic treatment-naive patients, although genotyping may impact the preferred treatment approach, it is not required if a pangenotypic regimen is used.

Appendix E: 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
Genotype 1-6: Without cirrhosis or with compensated cirrhosis, treatment-naïve or treatment-experienced* patient	One tablet PO QD for 12 weeks	Adult/Peds ≥ 30 kg: sofosbuvir 400 mg /velpatasvir 100 mg (one tablet) per day;	FDA-approved labeling

Indication	Dosing Regimen	Maximum Dose	Reference
Genotype 1-6: With decompensated cirrhosis, treatment-naïve or treatment-experienced* patient	One tablet PO QD with weight-based RBV for 12 weeks (RBV-ineligible patient may use: one tablet PO QD for 24 weeks)ǂ	Peds 17 to < 30 kg: sofosbuvir 200 mg /velpatasvir 50 mg per day; Peds < 17 kg: sofosbuvir 150 mg /velpatasvir 37.5 mg per day	
Genotype 1-6: Treatment-naïve and treatment-experienced patients, post-liver transplant with compensated cirrhosis or without cirrhosis	One tablet PO QD for 12 weeks		
Genotype 1-6: With decompensated cirrhosis in whom prior sofosbuvir- or NS5A inhibitor-based treatment failed	One tablet PO QD with weight-based RBV for 24 weeksǂ	One tablet (sofosbuvir 400mg /velpatasvir 100 mg) per day	AASLD-IDSA (updated October 2022)
Genotype 1-6: Treatment-naïve and treatment-experienced patients, post-liver transplant with decompensated cirrhosis	One tablet PO QD with RBV (starting at 600 mg and increased as tolerated) for 12 weeks (treatment naïve) or 24 weeks (treatment experienced)ǂ		
Genotype 3 with NS5A Y93H polymorphism: Treatment-naïve with compensated cirrhosis or treatment-experienced* without cirrhosis patient	One tablet PO QD with weight-based RBV for 12 weeksǂ		

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.
**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*

V. Product Availability

- Tablets: sofosbuvir 400 mg with velpatasvir 100 mg, sofosbuvir 200 mg with velpatasvir 50 mg
- Oral pellets: sofosbuvir 200 mg with velpatasvir 50 mg, sofosbuvir 150 mg with velpatasvir 37.5 mg

VI. References

1. Epclusa Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; April 2022. Available at: https://hcp.epclusa.com/. 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	Plan Approval Date
New policy created, split from CP.PHAR.17 Hepatitis C Therapies policy. HCV RNA levels over six-month period added to confirm infection is chronic.Life expectancy "≥12 months if HCC and awaiting transplant" is modified to indicate "≥12 months with HCV therapy." Methods to diagnose fibrosis/cirrhosis are modified to require a liver biopsy or a combination of one serologic and one radiologic test. Serologic and radiologic tests are updated and correlated with METAVIR per Appendix C. Dosing regimens are presented in Appendix. Criteria is added requiring a verification of HCV RNA status at 4 weeks (and again at 6 weeks if present at 4) accordingly, the initial approval period is shortened to 8 weeks.	07/16	07/16
Edited policy so congruent with the other HCV policies as follows: Testing criteria reorganized by cirrhosis status consistent with the regimen tables; HCC population broadened to incorporate those amenable to curative measures (resection, ablation, transplant). Fibrosure test that meets F3 requirement changed to ≥ 0.59. Criteria added excluding post-liver transplantation unless regimens specifically designate. Preferencing language edited for clarity. Removed creatinine clearance restriction. Under continuing approval, presence of HCV RNA is edited to remove specific timing of testing. Appendix B edited for clairity; Appendix C added. Appendix D – genotype "1" is footnoted to clarify possible subtypes. "Includes HCC" is removed from the decompensated cirrhosis. "Daily" is removed from the "recommended regimen" column; presentation of other data is abbreviated/short-handed.	08/16	09/16
Removed criteria regarding medication prescribed by a specialist Remove criteria regarding having HCC or advanced liver disease Removed criteria regarding medication adherence program Removed criteria regarding sobriety from alcohol/illicit drugs	9/16	9/2016
Added availability of full course of therapy as initial therapy consistent with appendix recommendation for initial criteria Removed continuation criteria	4/17	4/17

Reviews, Revisions, and Approvals	Date	Plan Approval Date
Added preferencing information requiring Mavyret for FDA-approved indications. Added information requiring Hep B screening for all patients prior to treatment to ensure that proper risk reduction measures are taken.	9/17	9/17
Annual review. No changes made.	3/18	3/18
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. In the initial approval criteria, changed RNA detectable period from "over a 6 month period" to "in the last 6 months" for infection diagnosis.	10/19	10/19
Added preferencing for AG Epclusa; Removed redirection to Mavyret based on contraindications criteria and all other information relative to Mavyret. Removed Appendix C for Metavir scoring. Updated order of all other Appendices. Updated references.	4/2020	4/2020
Added pediatric indication and dosing. References reviewed and updated.	7/2020	7/2020
Annual review. Added hepatitis B box warning to Appendix B 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. Updated Dosage and Administration table to include pediatric dosing when applicable, FDA-labeled dosing for post-liver transplant setting, references and grammatical updates. Added an additional tablet strength under product availability. Changed Centene Logo to PSHP Logo. References reviewed and updated.	4/2021	4/2021
Revised medical justification language for not using authorized generic version of Epclusa to "must use" language; updated Section III table with AASLD recommended regimens; references reviewed and updated.	7/2021	7/2021
Minor updating for correct order of lettering under Initial Criteria #10	8/2021	8/2021
Added a Diagnoses/Indications for which coverage is NOT authorized section to be consistent with corporate. Made minor formatting changes. updated Section V table with AASLD recommended regimens; RT4: updated criteria for Epclusa pediatric age expansion to 3 years and older along with pediatric dosing and new oral pellet dosage formulation; references reviewed and updated.	1/2022	1/2022
3Q 2022 annual review. References reviewed and updated.	7/2022	7/2022

Reviews, Revisions, and Approvals	Date	Plan Approval Date
Added criterion for NS5A RAS test for specific genotype 3 scenarios per AASLD recommendation. Template changes applied to other diagnoses/indications.	1/2023	1/2023
3Q 2023 annual review. Added a bypass for HCV genotype documentation if member is treatment-naïve and does not have cirrhosis (i.e., eligible for AASLD-IDSA simplified treatment regimen), also added accompanying rationale in Appendix E; corrected genotype 3 lab test scenario from "and" to "or"; references reviewed and updated.	7/2023	7/2023
3Q 2024 annual review: revised policy/criteria section to also include generic sofosbuvir/velpatasvir; removed qualifier of "chronic" from HCV criteria as AASLD-IDSA recommends treatment of both acute and chronic HCV; added Appendix E 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.