BlueCross BlueShield Arizona

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PHARMACY COVERAGE GUIDELINE

DIRECT ACTING ANTIVIRAL AGENTS FOR HEPATITIS C VIRUS (HCV): EPCLUSA® (sofosbuvir, velpatasvir) Sofosbuvir with velpatasvir (generic) HARVONI® (ledipasvir, sofosbuvir) Ledipasvir with sofosbuvir (generic) MAVYRET™ (glecaprevir, pibrentasvir) SOVALDI™ (sofosbuvir) VOSEVI™ (sofosbuvir, velpatasvir, voxilaprevir) ZEPATIER™ (elbasvir, grazoprevir) Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):

- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope

- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance

- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

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DIRECT ACTING ANTIVIRAL AGENTS FOR HEPATITIS C VIRUS (HCV)

Medical Necessity Requirements for EPCLUSA, HARVONI, MAVYRET, SOVALDI, VOSEVI, ZEPATIER, Ledipasvir-Sofosbuvir generic, Sofosbuvir-Velpatasvir generic

Hepatitis C Treatment Naive – Oral Agents						
	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6
Epclusa	X	X	X	X	X	X
Harvoni	X			X	X	X
Mavyret†	X	X	X	X	X	X
Sovaldi	X¶	X¶*	X¶*	X¶		
Vosevi	X	X	X	X	X	X
Zepatier	X			X		

Harvoni is not FDA approved for genotypes 2,3
† No cirrhosis or compensated cirrhosis (Child-Pugh A)
¶ Adult
* Child 3 years and older

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by a physician specializing in the diagnosis or in consultation with a Gastroenterologist, Hepatologist, or Infectious Disease provider

Indication

- Confirmed diagnosis of chronic hepatitis C virus (HCV) infection

Age Requirement

- Age and weight is consistent with FDA-label

Baseline Clinical Evaluation

- Documentation of liver fibrosis and cirrhosis assessment, including whether liver function is compensated or decompensated
- HCV genotype and baseline viral load within the previous 90 days
- Total bilirubin, albumin, INR, CrCl or GFR, LFTs, CBC within the previous 90 days
- Hepatitis A and B vaccination or laboratory evidence of immunity
- Testing for other significant viral illnesses within the previous 90 days and treatment plan if positive
- Negative pregnancy test in a woman of childbearing potential unless using adequate contraception
- List of previous HCV treatment(s) and the response(s) to these treatment(s) is available
- History of adherence with previous HCV treatment and/or current drug therapy

- Requested treatment regimen is consistent with product labeling, current clinical guideline recommendation from AASLD / IDSA for the specific HCV genotype, liver evaluation, treatment status, prior treatment history, and comorbidities

Alternative Therapies

- **For Zepatier:** Failure, contraindication, or intolerance to **TWO** of the following:
  - Epclusa or generic sofosbuvir with velpatasvir
  - Harvoni or generic ledipasvir with sofosbuvir
  - Mavyret
- **For HCV treatment requiring concurrent use of ribavirin and not currently on ribavirin:** Failure, contraindication, or intolerance to **generic ribavirin 200 mg**

Safety

- No FDA-labeled contraindications for use of requested agents
- No significant interacting drugs for use of requested agents

Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results:
    1. HCV genotype and baseline viral load
    2. Total bilirubin, albumin, INR, creatinine clearance or glomerular filtration rate, liver function tests, complete blood count
    3. Pregnancy test (if applicable)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration:

- Determined by HCV genotype and individual-specific factors
- Prescribing provider must submit viral load after 12 weeks of completion of therapy (SVR12)

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

PHARMACY COVERAGE GUIDELINE

DIRECT ACTING ANTIVIRAL AGENTS FOR HEPATITIS C VIRUS (HCV)

Description:

The presence of hepatitis C (HCV) antibody and HCV RNA are used to support a diagnosis of HCV infection. There are at least six major genotypes and several subtypes of HCV. Baseline viral load by quantitative assay and genotype are necessary to guide therapeutic options.
Hepatitis C infection is a major cause of chronic liver disease and a leading reason for liver transplantation. Sequelae of chronic hepatitis may include liver fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma. Hepatocellular carcinoma rarely progresses without underlying fibrosis and cirrhosis.
During acute HCV infection, there is a 20-50% chance of spontaneous resolution of infection. In at least two-thirds of individuals, this will occur within 6 months of the estimated time of infection; only 11% of those who remain viremic at 6 months will spontaneously clear infection at some time later.

Treatment of HCV is rapidly evolving, and clinical practice guidelines change as new agents and results of clinical studies become available. Newer agents alone or used in combination with other agents attempt to improve sustained virologic response (SVR) rates, reduce pill-burden, reduce drug-drug interactions, and improve patient tolerance to the medication. The American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) jointly publish a guideline on the treatment of HCV that can be accessed at http://www.hcvguidelines.org/full-report-view. The guideline has recommendations for testing, managing, and treating all HCV genotypes. Treatment options should consider patient-specific factors such as HCV genotype, prior treatment history, presence, or absence of compensated or decompensated cirrhosis. The guidance uses evidence-based information.

Ribavirin in combination with an interferon or non-interferon oral anti-hepatitis C antiviral medications is indicated for the treatment of chronic hepatitis C viral (HCV) infection in patients with compensated liver disease. Ribavirin is a synthetic nucleoside analog (purine analog) with antiviral activity. It inhibits replication of RNA and DNA viruses; it inhibits influenza virus RNA polymerase activity, and it inhibits the initiation and elongation of RNA fragments resulting in inhibition of viral protein synthesis.

HCV is an RNA virus that utilizes several important enzymes for reproduction. One is a NS3/4A serine protease enzyme that acts to cut large HCV encoded proteins into smaller pieces that are used to build new viruses. It is essential for viral replication. An additional enzyme that is essential for viral replication is NS5B RNA-dependent RNA polymerase that synthesizes the viral genome. The RNA polymerase initiates RNA synthesis by forming a bond between nucleotides that also begins the elongation process of RNA synthesis. A third enzyme, NS5A functions through interaction with other NS viral proteins and other cellular proteins that play a role in mediating host cell function and HCV viral replication, assembly, and egress Cross-resistance is possible between HCV NS3/4A protease inhibitors and between HCV NS5A inhibitors by class.

About 10-15% of HCV genotype 1 infected patients without prior exposure to NS5A inhibitors will have detectable HCV NS5A resistance associated substitutions (RASs) prior to treatment. The presence of baseline NS5A RASs can cause a substantial reduction in the activity (> 5-fold) of NS5A inhibitors that potentially adversely impact response to NS5A containing regimens. Given that baseline NS5A RASs are one of the strongest pretreatment predictors of treatment outcome with certain regimens, testing for these RASs prior to deciding on a therapeutic course is now recommended in select situations. Patients with genotype 1a may have higher rates of failure than genotype 1b and RASs testing is recommended for

genotype 1a. If the genotype cannot be subtyped recommendations from AASLD is to treat as a genotype 1a infection.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Per FDA-label, indicated age of:

- 18 years of age or older: Vosevi
- 12 years of age or older: Zepatier
- 3 years of age or older: Epclusa and generic, Harvoni and generic, Mavyret, and Sovaldi

Direct acting antiviral agents for hepatitis C, oral:

NS3/4A serine protease inhibitors:

Glecaprevir – found in Mavyret
Grazoprevir – found in Zepatier
Voxilaprevir – found in Vosevi

NS5A inhibitors:

Elbasvir – found in Zepatier
Ledipasvir – found in Harvoni
Pibrentasvir – found in Mavyret
Velpatasvir – found in Epclusa, Vosevi

NS5B polymerase inhibitors:

Dasabuvir – non-nucleoside inhibitor found in Viekira Pak
Sofosbuvir – nucleotide inhibitor found in Sovaldi, Harvoni, Epclusa, and Vosevi

The Child-Pugh classification system:

The Child-Pugh classification is a scoring system used to determine the prognosis of chronic liver disease and cirrhosis. Scoring is based upon several factors: albumin, total bilirubin, prothrombin time or international normalized ratio, and degrees of ascites and encephalopathy

Child-Pugh Classification of severity of liver disease			
Child-Pugh Classification	Points		
A: Well compensated	5-6		
B: Significant functional compromise	7-9		
C: Decompensated	10-15		
Parameter/Factor	1 point each	2 points each	3 points each
Total Bilirubin, mg/dL (or µmol/L)	< 2 (or < 34)	2-3 (or 34-50)	>3 or (> 50)
Albumin, g/dL (or g/L)	>3.5 (or > 35)	2.8-3.5 (or 28-35)	< 2.8 (or < 28)
Prothrombin time prolongation:			
Seconds over control	1-3	4-6	> 6
INR	< 1.7	1.71-2.3	> 2.3

Ascites	Absent	Slight/Mild	Moderate to severe
Encephalopathy	None	Grade 1-2 (or suppressed with medication)	Grade 3-4 (or refractory)

Ribavirin intolerance or ineligibility – requirements

Platelets < 50,000 cell/mm^3
Neutrophils < 750 cell/mm^3
Hemoglobin < 10 g/dL
Autoimmune hepatitis or other autoimmune condition known to be exacerbated by ribavirin
Pregnancy
Hemoglobinopathies
Creatinine clearance less than 50 mL/min
Coadministration with didanosine
Known hypersensitivity reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme)

Resources:

Epclusa (velpatasvir-sofosbuvir) product information, revised by Gilead Sciences, Inc. 04-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Sofosbuvir-velpatasvir product information, revised by Asegua Therapeutics LLC 04-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Harvoni (ledipasvir-sofosbuvir) product information, revised by Gilead Sciences, Inc. 12-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Ledipasvir-sofosbuvir product information, revised by Asegua Therapeutics LLC 12-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Mavyret (glecaprevir-pibrentasvir) product information, revised by AbbVie Inc. 10-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Sovaldi (sofosbuvir) product information, revised by Gilead Sciences, Inc. 12-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Vosevi (sofosbuvir-velpatasvir-voxilaprevir) product information, revised by Gilead Sciences, Inc. 11-2019. Available at DailyMed http://dailymed.nlm.nih.gov. February 18, 2025.

Zepatier (elbasvir-grazoprevir) product information, revised by Merck Sharp & Dohme Corp. 05-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Ribavirin capsule product information, revised by Aurobindo Pharma Limited. 07-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed March 24, 2025.

Ribavirin tablet product information, revised by Aurobindo Pharma Limited. 05-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed March 24, 2025.

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Muir AJ, Graham CS. Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults. In: UpToDate, DiBisceglie AM, Bloom A (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated January 24, 2024. Accessed March 24, 2025.

Graham CS, Muir AJ. Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults. In: UpToDate, DiBisceglie AM, Bloom A (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated January 23, 2025. Accessed March 24, 2025.

Feld JJ. Clinical manifestations, diagnosis, and treatment of acute hepatitis C virus infection in adults. In: UpToDate, DiBisceglie AM, Bloom A (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated August 07, 2024. March 24, 2025.

Chopra S, Arora S. Patient evaluation and selection for antiviral therapy chronic hepatitis C virus infection. In: UpToDate, DiBisceglie AM, Bloom A (Eds), UpToDate, Waltham MA.: UpToDate Inc. Literature current through February 2025. Topic last updated January 23, 2025. Available at http://uptodate.com. Accessed March 24, 2025.

Cartwright EJ, Pierret C, Minassian C, et al.: Alcohol use and sustained virologic response to hepatitis C virus direct-acting antiviral therapy. JAMA Network Open. 2023;6(9):e2335715. doi:10.1001/jamanetworkopen.2023.35715. Accessed April 30, 2024. Re-evaluated March 24, 2025.

AASLD/IDSA/IAS. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. http://www.hcvguidelines.org/contents. Last updated December 19, 2023. Accessed March 24, 2025.