

## PHARMACY POLICY – 5.01.606

# Hepatitis C Antiviral Therapy

Effective Date: Jan. 1, 2025

Last Revised: Dec. 10, 2024


Replaces: 5.01.11

RELATED MEDICAL POLICIES:

5.01.636 Chronic Hepatitis B Antiviral Therapy

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [DOCUMENTATION REQUIREMENTS](#) | [CODING](#)  
[RELATED INFORMATION](#) | [EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

 Clicking this icon returns you to the hyperlinks menu above.

---

## Introduction

Hepatitis C is caused by a virus that infects the liver. Sometimes the virus clears up on its own within a few months. This is called acute hepatitis C. In other cases, the infection lasts a long time. This is known as chronic hepatitis C. A person might be unaware of chronic hepatitis C because in the early stages the infection usually shows no symptoms or very mild symptoms. The drugs used to treat hepatitis C vary, but most of the newer antiviral drugs require a genetic test. This is because hepatitis C has different genetic types and certain drugs target specific genetic types. Other factors determining which drug may be recommended is whether other drugs were tried first and the status of a person's current medical condition. This policy describes the criteria when hepatitis C drugs may be considered medically necessary.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

---

**This policy contains separate criteria to be used based on the member's formulary. Please check the member Plan booklet or member ID card for coverage and click the links below to navigate to the appropriate section:**

**Section 1: Non-Metallic Formulary Plans (Rx Plan A1, A2, B3, B4, C4, E1, E3, E4, F1, and G3) and Plans with No Pharmacy Benefit Coverage**

**Section 2: Individual/Small Group/Student ISHIP Metallic Formulary Plans (Rx Plan M1, M2, and M4)**

## **Prioritizing Individuals for Treatment for Chronic Hepatitis C**

New direct-acting antiviral agents (DAA) are revolutionizing treatment for Hepatitis C. Clinical trials for these regimens have demonstrated sustained viral response rates (SVR) of greater than 90% except in the most complicated individuals.

Combined American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidelines for the treatment of chronic hepatitis C are available online at <http://www.hcvguidelines.org>. Due to the rapidly advancing clinical evidence, these guidelines are updated frequently. Refer to this resource for the most up-to-date information.

Treatment for chronic active hepatitis C may be considered medically necessary, as outlined in the most recent AASLD/IDSA guidelines, except as noted under the "Preferred Therapies" table below:

**The following section applies to non-Metallic formulary plans (Rx Plan A1, A2, B3, B4, C4, E1, E3, E4, F1, and G3) and plans with no pharmacy benefit coverage only. Please refer to the member plan booklet or member ID card.**

**Section 1: Non-Metallic Formulary Plans (Rx Plan A1, A2, B3, B4, C4, E1, E3, E4, F1, and G3) and Plans with No Pharmacy Benefit Coverage ONLY**

### **Preferred Therapies**

**Epclusa (sofosbuvir-velpatasvir), Harvoni (ledipasvir-sofosbuvir), Mavyret (glecaprevir-pibrentasvir), Sovaldi (sofosbuvir), and Vosevi (sofosbuvir-velpatasvir-voxilaprevir) are preferred over all other direct-acting antiviral (DAA) treatments including brand ledipasvir-sofosbuvir, brand sofosbuvir-velpatasvir, and Zepatier (elbasvir-grazoprevir) for the**



**Section 1: Non-Metallic Formulary Plans (Rx Plan A1, A2, B3, B4, C4, E1, E3, E4, F1, and G3) and Plans with No Pharmacy Benefit Coverage ONLY**

**Preferred Therapies**

**treatment of individuals with chronic hepatitis C infection without cirrhosis or with compensated cirrhosis (Child-Pugh A).**

**DAA treatment experienced individuals may be treated with Vosevi (sofosbuvir-velpatasvir-voxilaprevir) or Zepatier (elbasvir-grazoprevir) according to the current AASLD and IDSA guideline recommendations, taking into consideration known resistance-associated substitutions (RASs).**

**Exceptions:**

- The use of other regimen is considered not medically necessary, since equally or more effective alternative treatments are available at lower cost, **unless** analysis of RASs indicates that none of the above preferred combinations will likely be effective. In such cases, treatment according to the guidelines may be considered medically necessary.
- Individuals with more advanced cirrhosis (Child-Pugh B or C) should be treated according to current guideline recommendations (ideally in a liver transplant center).
- Treatment with other regimens for individuals with special circumstances not meeting the above criteria will be evaluated on an individual case basis.

**The following section applies to Individual and Small Group Metallic Formulary Plans (Rx Plan M1, M2, and M4) only. Please refer to the member's Plan.**

**Section 2: Individual/Small Group/Student ISHIP METALLIC Formulary Plans (Rx Plan M1, M2, and M4) ONLY**

**Preferred Therapies**

**Epclusa (sofosbuvir-velpatasvir), Harvoni (ledipasvir-sofosbuvir), Vosevi (sofosbuvir-velpatasvir-voxilaprevir), and Zepatier (elbasvir-grazoprevir) are preferred over all other direct-acting antiviral (DAA) treatments including brand ledipasvir-sofosbuvir, Mavyret (glecaprevir-pibrentasvir), brand sofosbuvir-velpatasvir, and Sovaldi (sofosbuvir) for the treatment of individuals with chronic hepatitis C infection without cirrhosis or with compensated cirrhosis (Child-Pugh A).**

**DAA treatment experienced individuals may be treated with Vosevi (sofosbuvir-velpatasvir-voxilaprevir) or Zepatier (elbasvir-grazoprevir) according to the current AASLD and IDSA**



**Section 2: Individual/Small Group/Student ISHIP METALLIC Formulary Plans (Rx Plan M1, M2, and M4) ONLY**

**Preferred Therapies**

**guideline recommendations, taking into consideration known resistance-associated substitutions (RASs).**

**Exceptions:**

- The use of other regimen is considered not medically necessary, since equally or more effective alternative treatments are available at lower cost, **unless** analysis of RASs indicates that none of the above preferred combinations will likely be effective. In such cases, treatment according to the guidelines may be considered medically necessary.
- Individuals with more advanced cirrhosis (Child-Pugh B or C) should be treated according to current guideline recommendations (ideally in a liver transplant center).
- Treatment with other regimens for individuals with special circumstances not meeting the above criteria will be evaluated on an individual case basis.

**The following section applies to all formulary plans and plans with no pharmacy benefit coverage.**

Drug	Medical Necessity
<p><b>Pegylated interferons</b></p> <ul style="list-style-type: none"> <li>• <b>Pegasys (peginterferon alfa-2a)</b></li> <li>• <b>PegIntron (peginterferon alfa-2b)</b></li> </ul>	<p><b>Pegasys (peginterferon alfa-2a) and PegIntron (peginterferon alfa-2b) require prior authorization for the treatment of chronic hepatitis C. Use in accordance with current guidelines is required.</b></p>

Drug	Length of Therapy
<ul style="list-style-type: none"> <li>• <b>Epclusa (sofosbuvir-velpatasvir)</b></li> <li>• <b>Brand sofosbuvir-velpatasvir</b></li> </ul>	<ul style="list-style-type: none"> <li>• Epclusa (sofosbuvir-velpatasvir) and brand sofosbuvir-velpatasvir are approved by the US Food and Drug Administration (FDA) for a 12-week course of therapy for the treatment of adult and pediatric individuals aged 3 years and older with genotype 1, 2, 3, 4, 5, or 6 without cirrhosis or with compensated cirrhosis (Child-Pugh A).</li> <li>• Epclusa (sofosbuvir-velpatasvir) and brand sofosbuvir-velpatasvir are approved by the FDA for a 12-week course of therapy for the treatment of adult and pediatric individuals</li> </ul>



Drug	Length of Therapy
<ul style="list-style-type: none"> <li>• <b>Harvoni (ledipasvir-sofosbuvir)</b></li> <li>• <b>Brand ledipasvir-sofosbuvir</b></li> </ul>	<p>aged 3 years and older with genotype 1, 2, 3, 4, 5, or 6 with decompensated cirrhosis (Child-Pugh B or C) when used in combination with ribavirin.</p> <ul style="list-style-type: none"> <li>• Harvoni (ledipasvir/sofosbuvir) and brand ledipasvir-sofosbuvir are approved by the US Food and Drug Administration (FDA) for a 12-week course for adult and pediatric individuals aged 3 years and older who are: <ul style="list-style-type: none"> <li>○ Treatment-naïve with genotype 1 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A)</li> <li>○ Treatment-experienced with genotype 1 infection without cirrhosis</li> <li>○ Treatment-naïve and treatment-experienced with genotype 1 infection with decompensated cirrhosis (Child-Pugh B or C), in combination with ribavirin</li> <li>○ Treatment-naïve and treatment-experienced liver transplant recipients with genotype 1 or 4 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A), in combination with ribavirin</li> <li>○ Treatment-naïve and treatment-experienced genotype 4, 5, or 6 without cirrhosis or with compensated cirrhosis (Child-Pugh A)</li> </ul> </li> <li>• Harvoni (ledipasvir/sofosbuvir) and brand ledipasvir-sofosbuvir are approved by the FDA for a 24-week course for adult and pediatric individuals aged 3 years and older who are: <ul style="list-style-type: none"> <li>○ Treatment experienced with genotype 1 with compensated cirrhosis (Child-Pugh A)</li> </ul> </li> </ul>
<p><b>Mavyret (glecaprevir-pibrentasvir)</b></p>	<ul style="list-style-type: none"> <li>• Mavyret (glecaprevir/pibrentasvir) is approved by the US Food and Drug Administration (FDA) for an 8-week course of therapy in treatment naïve adult and pediatric individuals 3 years and older with genotype 1, 2, 3, 4, 5, or 6 without cirrhosis or with compensated cirrhosis (Child-Pugh A).</li> <li>• FDA approved a 12-week course of treatment for treatment-experienced genotype 1 adult and pediatric individuals 3 years and older, without cirrhosis or with compensated cirrhosis (Child-Pugh A), having had earlier DAA regimens with an NS3/4A PI without prior treatment with an NS5A inhibitor.</li> </ul>



Drug	Length of Therapy
	<ul style="list-style-type: none"> <li>• FDA approved a 16-week course of treatment for treatment-experienced genotype 1 adult and pediatric individuals 3 years and older, without cirrhosis or with compensated cirrhosis (Child-Pugh A), having had earlier DAA regimens with an NS5A without prior treatment with an NS3/4A PI inhibitor.</li> <li>• Genotype 3 adult and pediatric individuals 3 years and older, without cirrhosis or with compensated cirrhosis (Child-Pugh A), and with prior treatment with pegylated interferon, ribavirin, and/or sofosbuvir but no prior treatment experience with an NS3/4A PI or NS5A inhibitor should receive 16 weeks.</li> <li>• Genotype 1, 2, 4, 5, or 6 adult and pediatric individuals 3 years and older without cirrhosis and with prior treatment with pegylated interferon, ribavirin, and/or sofosbuvir but no prior treatment experience with an NS3/4A PI or NS5A inhibitor should receive 8 weeks.</li> <li>• Genotype 1, 2, 4, 5, or 6 adult and pediatric individuals 3 years and older with compensated cirrhosis (Child-Pugh A) and with prior treatment with pegylated interferon, ribavirin, and/or sofosbuvir but no prior treatment experience with an NS3/4A PI or NS5A inhibitor should receive 12 weeks.</li> </ul>
<b>Sovaldi (sofosbuvir)</b>	<ul style="list-style-type: none"> <li>• Sovaldi (sofosbuvir) is approved by the US Food and Drug Administration (FDA) for a 12-week course for the treatment of adult individuals without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have: <ul style="list-style-type: none"> <li>○ Genotype 1 and 4 and Sovaldi (sofosbuvir) will be used in combination with peginterferon alfa and ribavirin</li> <li>○ Genotype 2 and Sovaldi (sofosbuvir) will be used in combination with ribavirin</li> </ul> </li> <li>• Sovaldi (sofosbuvir) is approved by the US Food and Drug Administration (FDA) for a 24-week course for the treatment of adult individuals without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have genotype 3 and Sovaldi (sofosbuvir) will be used in combination with ribavirin</li> </ul>



Drug	Length of Therapy
<b>Vosevi (sofosbuvir, velpatasvir, and voxilaprevir)</b>	<ul style="list-style-type: none"> <li>• Vosevi (sofosbuvir, velpatasvir, and voxilaprevir) is approved by the US Food and Drug Administration (FDA) for a 12-week course for the treatment of adult individuals without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have:               <ul style="list-style-type: none"> <li>○ Genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor.</li> <li>○ Genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.</li> </ul> </li> </ul>
<b>Zepatier (elbasvir-grazoprevir)</b>	<ul style="list-style-type: none"> <li>• Zepatier (elbasvir-grazoprevir) is approved by the US Food and Drug Administration (FDA) for a 12-week course for the treatment of individuals aged 12 years and older without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have:               <ul style="list-style-type: none"> <li>○ Genotype 1a and are treatment-naïve or peginterferon alfa and ribavirin experienced without baseline NS5A polymorphisms</li> <li>○ Genotype 1b and are treatment-naïve or peginterferon alfa and ribavirin experienced</li> <li>○ Genotype 1a or 1b and are peginterferon alfa, ribavirin, and HCV NS3/4A proteinase inhibitor experienced when used in combination with ribavirin</li> <li>○ Genotype 4 and are treatment naïve</li> </ul> </li>   <li>• Zepatier (elbasvir-grazoprevir) is approved by the US Food and Drug Administration (FDA) for a 16-week course for the treatment of individuals aged 12 years and older without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have:               <ul style="list-style-type: none"> <li>○ Genotype 1a and are treatment-naïve or peginterferon alfa and ribavirin experienced with baseline NS5A polymorphisms</li> <li>○ Genotype 4 and are peginterferon alfa and ribavirin experienced when used in combination with ribavirin</li> </ul> </li> </ul>



Drug	Length of Therapy
Deviations from AASLD/IDSA guidelines	All other deviations from the length of therapy recommended by the AASLD/IDSA guidelines are considered investigational.

Drug	Investigational
As listed	The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.

Documentation Requirements
<p>The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:</p> <ul style="list-style-type: none"> <li>Office visit notes that contain the diagnosis, relevant history, physical evaluation, genotyping of hepatitis C virus, length of requested therapy, and medication history</li> </ul>

## Coding

N/A

## Related Information

### Viral Genotyping

Genotyping of hepatitis C virus is considered medically necessary when used according to current guideline recommendations.

### Resistance Mutations (Resistance-Associated Substitutions, or RASs)

Genetic testing for resistance mutations is commercially available and is considered medically necessary to guide the selection of an individual-specific direct-acting antiviral agents (DAA) regimen in circumstances where it is recommended by the current guidelines.





## Hepatitis C

Approximately 4 million Americans have been infected with hepatitis C virus (HCV), of whom 74% have chronic infection. Most individuals are diagnosed based on elevated liver transaminases and the presence of hepatitis C virus ribonucleic acid (HCV RNA). Hepatitis C is a major cause of liver-related morbidity and mortality. Although the disease typically progresses without symptoms for several decades, 20% to 30% of infected individuals develop cirrhosis within 10 to 20 years and 5% to 10% develop end stage liver disease. After development of cirrhosis, the annual risk of development of hepatocellular carcinoma is 1% to 4%. Chronic hepatitis C is also the most common indication for liver transplantation in the United States.

There are 6 known genotypes and over 50 subtypes of HCV. These genotypes vary by as much as 34% in their genetic sequencing and subtypes are known to differ by 20% to 23%. This genetic heterogeneity has known implications for therapeutic management and its effectiveness. Genotypes 1 and 4 are associated with less chance of achieving a sustained virologic response (SVR) or the clearance of HCV RNA by qualitative analysis 24 weeks after therapy cessation. Although SVR is a surrogate endpoint which has not yet been correlated with improved survival, it is the current standard measure of response to therapy.

Various DAAs have been approved. DAAs are administered orally, tend to have fewer side effects and achieve higher SVR rates with shorter courses of therapy. The most recently approved products have pangenotypic coverage. They are Mavyret (glecaprevir/pibrentasvir), Vosevi (sofosbuvir/velpatasvir/voxilaprevir) and Epclusa (sofosbuvir/velpatasvir).

## Benefit Application

This policy is managed through the pharmacy benefit.

## Evidence Review

---

### Sustained Virologic Response-Chronic Hepatitis C

Although sustained virologic response (SVR) is a surrogate endpoint, it has recently been correlated with improved survival, and it is the current gold standard measure of response to



chronic hepatitis C virus (HCV) pharmacotherapy. An SVR is the clearance of HCV ribonucleic acid (RNA) by qualitative analysis 24 weeks after therapy cessation. Pretreatment factors associated with achievement of SVR include lower body mass indexes (body weight <75 kg), milder histology on liver biopsy (Metavir fibrosis stage 0 or 1), genotype 2 or 3, and lower initial viral titers (HCV RNA level <2 million copies/mL or 800,000 IU/mL). During treatment, factors associated with achievement of an SVR include rapid or early virologic response, therapy adherence, and lack of human immunodeficiency virus (HIV) co-infection. Achievement of an SVR has been associated with resolution of liver injury, reduction in hepatic fibrosis, a low likelihood of relapse, and survival.

## **Adherence-Chronic Hepatitis C**

Adherence is important to chronic HCV treatment success. The currently recommended all-direct-acting antiviral agent (DAA) regimens are orally administered with convenient dosing regimens and have much fewer side effects, compared to the older regimens. Sustained viral response is achieved in over 95% of individuals in most subpopulations in clinical trials. Real world retrospective analyses confirm fairly similar SVR rates outside of controlled trial settings.

Non-adherence is the principal reason for failure with these highly effective treatments; therefore, individuals should be screened for poor adherence risks. All individuals should be strongly encouraged to follow the directions from their prescriber. Those having difficulty with side effects should discuss these concerns with their prescriber or pharmacist.

## **Early Virologic Response-Chronic Hepatitis C**

Early virologic response (EVR) is defined as clearance of HCV-RNA during the first 12 weeks of therapy. A partial response is defined as a minimum 2-log decrease in hepatitis C viral load after 12 weeks of therapy.

## **Relapse and Non-Response-Chronic Hepatitis C**

Relapse is defined as initial achievement of an SVR that is not sustained over time. Non-response is defined as never achieving an SVR. Guidelines for retreatment of this population are evolving rapidly. See <http://www.hcvguidelines.org/>. Accessed December 12, 2024.



## Transplantation-Chronic Hepatitis C

Hepatitis C frequently recurs in the transplant setting. Guidelines for retreatment of this population are evolving rapidly. Treatment for post-transplant individuals or for those awaiting transplantation will be approved in accordance with current guideline recommendations. See <http://www.hcvguidelines.org>. Accessed December 12, 2024.

### Extended Treatment Intervals

Extended treatment is not normally advised with today's highly efficient regimens. Individuals failing to achieve SVR should be evaluated for retreatment with a guideline-appropriate regimen, rather than extending current treatment.

### Unique Populations

Providers treating individuals in these groups, e.g., HIV- and/or hepatitis B virus-coinfected individuals or those with other serious infections, individuals with decompensated cirrhosis, individuals with end stage renal disease, or children should consult the guidelines for the most current recommendations. Treatment for such cases is reviewed on an individual basis.

### Sofosbuvir/Velpatasvir Combination Product (Epclusa)

Four Phase-3 ASTRAL clinical trials demonstrated that a 12-week, fixed-dose, single-tablet regimen of sofosbuvir and velpatasvir (SOF/VEL 400/100 mg) achieved high sustained virologic responses (cures) for all hepatitis C genotypes. The primary efficacy endpoint for each of the four ASTRAL trials was a SVR, which was defined as an HCV RNA level of less than 15 IU/mL (undetectable) at 12 weeks after the end of treatment (SVR12). Viral loads <15 IU/mL are considered undetectable. Secondary endpoints included safety/tolerability, resistance, and additional efficacy outcomes.

ASTRAL-1 enrolled individuals with HCV genotypes 1, 2, 4, 5, and 6. Individuals received either SOF/VEL or placebo for 12 weeks. SOF/VEL taken once daily for 12 consecutive weeks produced cure rates of approximately 99% across all genotypes. Among the individuals enrolled in this trial, 121 participants had cirrhosis, and at the end of study, 120 of those participants (99%)



achieved SVR12. Also, 99% of the individuals with baseline NS5A resistance-associated variants (RAVs) had an SVR.

ASTRAL-2 assigned individuals with genotype 2 to either sofosbuvir + velpatasvir (SOF/VEL) for 12 weeks or sofosbuvir + ribavirin (SOF+RBV) for 12 weeks. 86% of individuals had previously been treated for HCV (treatment experienced). Treatment with SOF/VEL was superior to the SOF+RBV regimen. SVR was achieved in 99% of individuals in the SOF/VEL group, compared with an SVR of 94% in the SOF+RBV group. There were no cases of treatment failure despite the presence of baseline NS5A resistance-associated variants (RAVs).

ASTRAL-3 assigned individuals with genotype 3 to either SOF/VEL for 12 weeks or SOF+RBV for 24 weeks. Cirrhosis was present in 30% of individuals, and 74% of individuals had previous HCV treatment. The SVR12 rates were 95% with SOF/VEL and 80% with SOF+RBV. Of 43 study participants with baseline NS5A RAVs, 88% achieved SVR compared to 97% SVR in participants without resistance mutations. Note that all participants who had cirrhosis did not have symptoms associated with severe scarring of the liver, so cure rates were relatively high (99%). The combination of SOF/VEL led to higher SVR12 rates than 24 weeks of SOF/RBV and was very well tolerated. SOF/VEL for 12 weeks yielded high rates of SVR12 without the need for RBV.

ASTRAL-4 only enrolled individuals with decompensated cirrhosis, a more difficult group to cure. Individuals had genotypes 1, 2, 3, 4, and 6, and the majority of study participants (75%) had HCV genotype 1. Individuals were assigned to one of three treatment groups: SOF/VEL for 12 weeks, SOF/VEL + RBV for 12 weeks, or SOF/VEL for 24 weeks. The highest SVR rate was 94% in the SOF/VEL + RBV group vs 83% and 86% in the SOF/VEL 12-week and SOF/VEL 24-week groups, respectively. Overall, 8 out of 72 individuals with baseline NS5A RAVs experienced virologic failure (89% achieved SVR).

## **Glecaprevir/Pibrentasvir Combination Product (Mavyret)**

Glecaprevir/pibrentasvir (GLE/PIB) is a fixed dose, oral, pangenotypic combination NS3/4A protease inhibitor and NS5A inhibitor indicated for the treatment of chronic HCV in GT 1-6 without cirrhosis or with compensated cirrhosis (Child-Pugh A) and HCV GT 1 previously treated with NS5A inhibitors or NS3/4A protease inhibitors but not both. Mavyret was approved for an 8-week treatment regimen in individuals with treatment-naïve (GT 1-6) or experienced (GT 1, 2, 4, 5, 6; PEG-IFN, RBV, and/or SOF) chronic HCV. Additionally, Mavyret was approved for a 12-week regimen in individuals with GT 1-6 and compensated cirrhosis; GT 1 and prior NS3/4A protease inhibitor experience + cirrhosis; and GT 1, 2, 4, 5, 6 and prior PEG-IFN, RBV, and/or SOF experience with compensated cirrhosis. Mavyret was approved for a 16-week regimen in GT 1



individuals with prior NS5A inhibitor experience + cirrhosis; and GT 3 individuals with prior PEG-IFN, RBV and/or SOF experience + cirrhosis.

The regimen GLE/PIB has been studied in eight fair-quality, unpublished, phase 3 trials. Most trials were open-label with the exception of a single double-blind trial. A non-comparative trial design was used in three trials, four trials compared GLE/PIB to a historical SVR12 rate, and one trial included an active comparator. The GLE/PIB phase-3 trials showed good efficacy in a wide range of populations including HCV GT 1-6, compensated cirrhosis (excluding GT 3), human immunodeficiency virus (HIV) coinfection, chronic kidney disease (CKD), and transplant individuals (liver or renal). Overall, GLE/PIB was highly effective with an SVR12 ranging from 97% to 100% in the majority of trials. Exceptions were an SVR12 of 93% in individuals with HIV coinfection and compensated cirrhosis in GT 1-6, SVR12 of 95% in treatment-naïve GT 3 individuals, and SVR12 of 89%-92% in individuals with prior DAA treatment. Trial limitations with GLE/PIB included very little exposure to certain subgroups such as treatment-experienced or cirrhotic GT 3 or DAA-experienced individuals. Additionally, an 8-week regimen was assessed in three phase 3 trials among noncirrhotic individuals with GT 1 (treatment experienced or naïve), GT 3 (nonrandomized arm, treatment naïve only), and HIV coinfection (GT 1-6) with SVR12 of 99%, 95%, and 100%, respectively. Each of these trials met their respective goals for noninferiority for the 8-week regimen. Of note, data for use of an 8-week regimen among other populations came from phase 2 trials and was limited by a very low exposure among GT 4-6 individuals and an SVR12 of 93% with GT 4 individuals.

## **Sofosbuvir/Velpatasvir/Voxilaprevir Combination Product (Vosevi)**

Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) is a fixed dose, single-tablet, pangenotypic combination NS5B polymerase inhibitor, NS5A inhibitor, and NS3/4A protease inhibitor approved in July 2017 for the treatment of chronic hepatitis C virus (HCV) + compensated cirrhosis (Child-Pugh A) in individuals with 1) genotype (GT) 1-6 and prior NS5A inhibitor treatment and 2) for GT 1a and GT 3 with prior sofosbuvir (SOF) exposure without NS5A treatment. Vosevi was assessed in four published, fair quality, phase 3 trials (POLARIS 1-4). The majority of the trials were multicenter (MC), randomized, open-label (OL) trials which compared SOF-VEL-VOX to a prespecified performance standard. The POLARIS-1 and -4 trials assessed the efficacy of SOF-VEL-VOX (Vosevi) and SOF-VEL (Epclusa) for 12 weeks in comparison to a performance goal (sustained viral response [SVR] 85%). Polaris-1 included individuals with HCV GT 1-6 + compensated cirrhosis who had failed NS5A inhibitors while the POLARIS-4 trial included individuals with GT 1-3 + compensated cirrhosis who failed pegylated-interferon (PEG-



IFN) + ribavirin (RBV) + protease inhibitor (PI) or any direct-acting antiviral (DAA) other than NS5A inhibitors.

SOF-VEL-VOX met criteria for superiority compared to the performance goal with SVR12 of 96% and 98%, respectively, in both trials. Of note, SVR12 decreased to 93% in individuals with cirrhosis who failed NS5A treatment. Relapse following treatment occurred in <2% of SOF-VEL-VOX individuals with both trials. Of note, no difference in SVR12 was found between treatment groups (SOF-VEL-VOX and SOF-VEL) in individuals with GT 1b and 2 HCV in the POLARIS-4 trial. Consequently, Vosevi is indicated in GT 1a and 3 individuals only in this population. The POLARIS-2 and -3 trials assessed the efficacy of SOF-VEL-VOX for 8 or 12 weeks in DAA-naïve individuals with HCV GT 1-6 + cirrhosis. The 8-week regimen did not meet the prespecified performance goal in the POLARIS-2 trial (GT 1, 2, 4, 5, 6) with overall SVR12 of 95%. Vosevi did not receive approval for an 8-week regimen.

## Ledipasvir/Sofosbuvir Combination Product (Harvoni)

In the 3 Phase III clinical trials (the ION trials), the SVR rates of sofosbuvir/ledipasvir were found to be efficacious in treatment naïve individuals at 8 weeks (SVR rate 94%, 95% CI 90 to 97 in individuals without cirrhosis), 12 weeks (SVR rate 99%, 95% CI 96 to 100), and 24 weeks (SVR rate 98%, 95% CI 95 to 99). However, in the individuals who received 8-week treatment, a 10% relapse rate was seen in individuals who had a baseline HCV RNA load  $\geq 6$  million IU/mL leading to the FDA only recommending considering 8-week treatment in treatment naïve individuals whose viral load is < 6 million IU/mL. Treatment with sofosbuvir/ledipasvir was also found to be efficacious in treating individuals who are treatment experienced (treatment experienced = individuals who tried and failed pegIFN and ribavirin  $\pm$  a NS3/4a protease inhibitor) at 12 weeks and 24 weeks; SVR rates 94% (95% CI 87-97) and 99% (95% CI 95-100), respectively. In all of the studies, the addition of ribavirin added no significant increase in efficacy while generally increasing the adverse events (AEs) experienced in each individual group.

In regard to cirrhosis, treatment naïve individuals who were cirrhotic at baseline achieved similar response rates as those who had no cirrhosis at 12 and 24 weeks of sofosbuvir/ledipasvir treatment. Cirrhotic individuals were not part of the 8-week trial for treatment naïve individuals. The only distinguishing factor of predicting treatment response in treatment experienced individuals was cirrhosis. Individuals with baseline cirrhosis and treated with 12 weeks of sofosbuvir/ledipasvir had an SVR rate of 92% (95% CI 84 to 97) compared to an SVR rate of 98% (95% CI 96 to 99) for individuals without cirrhosis.



There are currently studies underway to evaluate sofosbuvir/ledipasvir in different HCV genotypes 1-6 and in individuals who have advanced liver disease and in individuals who have undergone liver transplant. There is also a study not yet in the recruiting phase designed to test the efficacy of sofosbuvir/ledipasvir in individuals co-infected with HIV. Currently there are no guidelines for the off-label use of sofosbuvir/ledipasvir in the above populations. Sofosbuvir is considered pan-genotypic in combination with ribavirin and pegIFN in all HCV genotypes 1-6.

There are no trials currently which compare the use of sofosbuvir/ledipasvir to current recommended sofosbuvir, ribavirin, and pegIFN. However, as stated in the studies, the typical SVR rate seen with standard therapy range around 60-70% for HCV genotype 1. In all sofosbuvir/ledipasvir studies, the SVR rates were >97% for the use of the product for the duration FDA has approved in each individual group.

Sofosbuvir/ledipasvir was generally safe over varying treatment lengths with the shorter the length of treatment resulting in fewer AE. More AE were seen in treatment arms of the studies that included ribavirin. No individuals discontinued treatment early due to AE in ION-2 (440 individuals). 10 individuals (out of 865) in ION-1 discontinued treatment early due to AE, 4 from the sofosbuvir/ledipasvir 24-week arm and 6 from the sofosbuvir/ledipasvir + ribavirin 24-week arm. There was no early discontinuation in either 12-week arm. In ION-3 (647 individuals), 3 individuals discontinued sofosbuvir/ledipasvir due to AE; 1 in the 8-week arm (due to road accident), 2 in the 12-week arm of sofosbuvir/ledipasvir (1 due to arthralgia and 1 due to lung cancer). Out of a total of 1952 individuals exposed to sofosbuvir/ledipasvir 13 individuals (<1%) discontinued treatment early due to AE. This is much lower than the standard discontinuation rate of interferon-based therapy. Mild to moderate AE were common across all trials (67 to 92% of individuals reported at least one AE). The most common AE were fatigue, headache, nausea, diarrhea, and insomnia.

## **Elbasvir and Grazoprevir (Zepatier)**

Zepatier combines two direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle.

Elbasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of elbasvir has been characterized based on cell culture antiviral activity and drug resistance mapping studies.

Grazoprevir is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, grazoprevir



inhibited the proteolytic activity of the recombinant HCV genotype 1a, 1b, and 4a NS3/4A protease enzymes with IC50 values of 7 pM, 4 pM, and 62 pM, respectively.

The efficacy of Zepatier was assessed in 2 placebo-controlled trials and 4 uncontrolled Phase 2 and 3 clinical trials in 1401 subjects with genotype (GT) 1, 4, or 6 chronic hepatitis C virus infection with compensated liver disease (with or without cirrhosis). An overview of the 6 trials (n=1373) contributing to the assessment of efficacy in genotype 1 or 4 is provided in Table 12. C-EDGE TN, C-EDGE COINFECTION, C-SCAPE, and C-EDGE TE also included subjects with genotype 6 HCV infection (n=28). Because Zepatier is not indicated for genotype 6 infection, results in individuals with genotype 6 infection are not included in clinical studies.

**Table 1. Trials Conducted with Zepatier**

<b>Trial</b>	<b>Population</b>	<b>Study Groups and Duration (Number of Subjects Treated)</b>
C-EDGE TN (double-blind)	GT1,4 TN with or without cirrhosis	ZEPATIER for 12 weeks (N=306) Placebo for 12 weeks (N=102)
C-EDGE COINFECTION (open-label)	GT 1, 4 TN with or without cirrhosis HCV/HIV-1 co-infection	ZEPATIER for 12 weeks (N=217)
C-SURFER (double-blind)	GT 1 TN or TE with or without cirrhosis Severe renal impairment including hemodialysis	EBR* + GZR* for 12 weeks (N=122) Placebo for 12 weeks (N=113)
C-SCAPE (open-label)	GT 4 TN without cirrhosis	EBR* + GZR* for 12 weeks (N=10) EBR* + GZR* + RBV for 12 weeks (N=10)
C-EDGE TE (open-label)	GT 1, 4 TE with or without cirrhosis HCV/HIV-1 co-infection	ZEPATIER for 12 or 16 weeks (N=105, and 101, respectively) ZEPATIER + RBV for 12 or 16 weeks (N=104 and 104, respectively)
C-SALVAGE (open-label)	GT 1 TE with HCV protease inhibitor regimen† with or without cirrhosis	EBR* + GZR* + RBV for 12 weeks (N=79)





GT = Genotype

TN = Treatment-Naïve

TE = Treatment-Experienced (failed prior treatment with interferon [IFN] or peginterferon alfa [PegIFN] with or without ribavirin [RBV] or were intolerant to prior therapy).

\*EBR = elbasvir 50 mg; GZR = grazoprevir 100 mg; EBR + GZR = co-administered as single agents.

† Failed prior treatment with boceprevir, telaprevir, or simeprevir in combination with PegIFN + RBV.

Zepatier was administered once daily by mouth in these trials. For subjects who received ribavirin (RBV), the RBV dosage was weight-based (less than 66 kg = 800 mg per day, 66 to 80 kg = 1000 mg per day, 81 to 105 kg = 1200 mg per day, greater than 105 kg = 1400 mg per day) administered by mouth in two divided doses with food.

Sustained virologic response (SVR) was the primary endpoint in all trials and was defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after the cessation of treatment (SVR12). Serum HCV RNA values were measured during these clinical trials using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with an LLOQ of 15 HCV RNA IU per mL, with the exception of C-SCAPE where the assay had an LLOQ of 25 HCV RNA IU per mL.

## 2007 Update

When Hepatitis C individuals receive a liver transplant, allograft infection is universal, and recurrent hepatitis C progresses at an accelerated rate. Preemptive antiviral therapy after transplantation has been disappointing. However, treatment of established histological disease with a combination of pegylated interferon and ribavirin is associated with sustained virologic response (SVR) in roughly 25% of cases. A recent meta-analysis reported a pooled SVR rate of 27% (range 23-31%). Stable and improved fibrosis scores can be expected in most individuals who achieve SVR. While these rates are not impressive, pegylated interferon plus ribavirin remains the best available treatment and represents the current standard of care. Further research in this area is clearly needed.

## 2008 Update

A literature search of the MEDLINE database did not identify any additional published studies that would prompt reconsideration of the policy statement, which remains unchanged.



## 2009 Update

A literature search of the MEDLINE database from May 2008 to March 2009 and the 2008 AASLD annual meeting proceedings did not identify any additional published studies that would result in major reconsideration of the policy statement, excepting results from the EPIC3 (Evaluation of PegIntron in Control of Hepatitis C Cirrhosis) study. EPIC3 is a multinational, open-label trial assessing the efficacy and safety of peginterferon alfa-2b 1.5 mcg/kg/wk in combination with weight-based ribavirin for 48 weeks in the retreatment of chronic hepatitis C individuals with fibrosis (METAVIR F2-F4) unresponsive to or relapsing after standard or pegylated interferon-alfa/ribavirin combination treatment. Overall, SVR rates were 7%, 6%, and 18% in Peg-2b, Peg-2a, and standard interferon combination therapy nonresponders and 32%, 34%, and 43% in Peg-2b, Peg-2a, and standard interferon combination therapy relapsers. Undetectable HCV-RNA at week 12 was the most important predictor of SVR in this population. Overall, 56% achieved SVR if HCV-RNA was undetectable vs. 5% achieved SVR if only a  $\geq 2$  log decrease in HCV-RNA was observed at week 12).

## 2010 Update

A literature search did not identify any additional published studies that would require reconsideration of the policy statement. The Policy Guidelines dealing with slow responders and also requests for more than 2 courses of retreatment per year were added based on expert consultation.

## 2011 Update

A literature search did not identify any additional published studies that would require reconsideration of the policy statement.

## 2012 Update

Added criteria for Hepatitis C protease inhibitors telaprevir and boceprevir, based on a review of the primary literature.



## 2014 Update

Two new antiviral agents were approved in late 2013. These agents are rapidly changing the standard of care for treating Hepatitis C.

## 2015 Update

One additional prioritization criterion was added to the list. A brief description of NASH and NAFLD has been added to the discussion section. Two new antiviral agents (Technivie and Daklinza) were approved at the end of July 2015.

## 2015 Update (August)

A new direct acting antiviral agent combination product was approved in December 2014. This product, Viekira Pak, consists of three active ingredients, paritaprevir (boosted by ritonavir), ombitasvir and dasabuvir.

## 2016 Update

One new agent (Zepatier), and its related criteria and clinical summary were added to the medical policy.

Restructuring of the policy and guidelines to reflect AASLD/IDSA recommendations.

## 2016 Update (December)

Step therapy criteria requiring the use of Harvoni before Epclusa can be approved (only when clinically appropriate) has been added to the EXCEPTIONS' section of the policy.

## 2017 Update (August)

Step therapy criteria requiring the use of Mavyret first line wherever 8- or 12-week courses of therapy are adequate. Other individuals may be treated with Epclusa or other agents, according



to AASLD/IDSA guidelines and case-based assessment of medical necessity. Vosevi added as salvage therapy in treatment experienced individuals with resistance to other regimens.

## **2017 Update (September)**

Step therapy criteria updated requiring the use of Mavyret, Epclusa or Harvoni first line wherever one or more of these is indicated.

## **2018 Update (November)**

Reviewed AASLD/IDSA guidelines update of May 24, 2018, which is the reference for these criteria. No changes were made to the guidelines that would affect these medical necessity criteria.

## **2019 Update (September)**

Reviewed the prescribing information for all drugs along with the AASLD/IDSA guidelines. The May 24, 2018 update remains the most current version of the AASLD/IDSA guidelines. No new evidence found that would change this policy.

## **2020 Update (December)**

Reviewed the prescribing information for all drugs listed in policy along with changes to the AASLD/IDSA guidelines. The AASLD/IDSA guidelines were last updated August 27, 2020. Epclusa (sofosbuvir/velpatasvir) has an expanded indication and now includes pediatric individuals aged 6 years and older or weighing at least 17 kg. Genotypes covered and 12-week treatment duration remains the same for pediatric individuals. Harvoni (ledipasvir/ sofosbuvir) has an expanded indication to include for all covered indications pediatric individuals aged 3 years and older. Removed note on Vosevi (sofosbuvir, velpatasvir, and voxilaprevir) being contraindicated for severe renal impairment. The updated prescribing information now states that no dosage adjustment of Vosevi is recommended for individuals with mild, moderate, or severe renal impairment, including ESRD requiring dialysis. Removed references within policy to Technivie and Daklinza as both products have been discontinued by manufacturer and are no longer available.



## 2021 Update (July)

Reviewed the prescribing information for all drugs listed in policy along with changes to the AASLD/IDSA guidelines. The AASLD/IDSA guidelines were last updated January 21, 2021. Mavyret (glecaprevir/pibrentasvir) has an expanded indication and now includes all pediatric individuals aged 3 years and older. Mavyret now has an oral pellet dosage form and is no longer restricted to individuals weighing at least 45 kg. Epclusa (sofosbuvir/velpatasvir) also has an expanded indication to include all pediatric individuals aged 3 years and older along with an oral pellet dosage form. Due to availability of an oral pellet dosage form Epclusa is no longer restricted to individuals weighing at least 17 kg. Updated Harvoni (ledipasvir/sofosbuvir) criteria to include length of therapy based on HCV genotype and individual population and updated Vosevi (sofosbuvir, velpatasvir, and voxilaprevir) criteria to document length of therapy is 12 weeks for all approved indications.

## 2022 Update (September)

Reviewed the prescribing information for all drugs listed in policy along with changes to the AASLD/IDSA guidelines. The AASLD/IDSA guidelines were last updated September 29, 2021. No changes were made to the guidelines that would affect these medical necessity criteria.

## 2023 Update (June)

Reviewed the prescribing information for all drugs listed in policy along with changes to the AASLD/IDSA guidelines. The AASLD/IDSA guidelines were last updated on October 24, 2022. No changes were made to the guidelines that would affect these medical necessity criteria.

## 2024 Update (June)

Reviewed the prescribing information for all drugs listed in policy along with changes to the AASLD/IDSA guidelines. The AASLD/IDSA guidelines were last updated on May 25, 2023. No changes were made to the guidelines that would affect these medical necessity criteria.



## 2024 Update (December)

Added FDA approved uses for brand sofosbuvir-velpatasvir, brand ledipasvir-sofosbuvir, Sovaldi (sofosbuvir) and Zepatier (elbasvir-grazoprevir). New policy section with headers added for Section 2 (individual/small group/student ISHIP Metallic formulary plans) with hyperlinks to aid navigation. Added separate coverage criteria for Metallic (individual/small group/student ISHIP plans) formulary members for the following drugs: Epclusa, brand ledipasvir-sofosbuvir, Harvoni, Mavyret, brand sofosbuvir-velpatasvir, Sovaldi, Vosevi, and Zepatier. For Section 1 (non-individual formulary plans), clarified that Sovaldi (sofosbuvir) and Vosevi (sofosbuvir-velpatasvir-voxilaprevir) are preferred products. For Section 1, indicated that Zepatier (elbasvir-grazoprevir) may be considered medically necessary for the treatment of DAA treatment experienced individuals according to the current AASLD and IDSA guideline recommendations. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

## References

1. Kim WR. The burden of hepatitis C in the US *Hepatology*. 2002; 36(5 suppl 1):S30-S34.
2. Yano M et al. The long-term pathological evolution of chronic hepatitis C. *Hepatology*. 1996; 23:1334-1340.
3. Pearlman BL. Hepatitis C treatment update. *Am J Med*. 2004; 117:344-352.
4. Anon. National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 2002 June 10-12. *Hepatology*. 2002; 36(5 suppl 1):S3-S20.
5. Muir AJ, Provenzale D. A descriptive evaluation of eligibility for therapy among veterans with chronic hepatitis C virus infection. *J Clin Gastroenterol*. 2002; 34:268-271.
6. Manns MP, McHutchison JG, Gordon SC et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet*. 2001; 358:958-965.
7. Fried MW, Shiffman ML, Redd R et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002; 347:975-982.
8. El-Surag HB, Mason AC. Risk factors for the rising rates of primary liver cancer in the United States. *Arch Intern Med*. 2000; 160:3227-3230.
9. United Network for Organ Sharing/Organ Procurement Transplant Network. <http://optn.transplant.hrsa.gov>. Accessed June 13, 2024.
10. Lindsay KL et al. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. *Hepatology*. 2001; 34:395-403.
11. Zeuzem S et al. Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med*. 2000; 343:1666-1672.



12. Poynard T, Marcellin P, Lee SS et al. Randomized trial of interferon alpha-2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha-2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). *Lancet*. 1998; 352:1426-1432.
13. McHutchison JG, Manns M, Patel K et al. Adherence to combination therapy enhances sustained viral response in genotype-one infected patients with chronic hepatitis C. *Gastroenterology*. 2002; 123:1061-1069.
14. Davis GL, Wong JB, McHutchison JG et al. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology*. 2003; 38: 645-652.
15. Wong JB, Davis GL, McHutchison Jg et al. Economic and clinical effects of evaluating rapid viral response to peginterferon alfa-2a plus ribavirin for the initial treatment of chronic hepatitis C. *Am J Gastroenterol*. 2003; 98:2354-2362.
16. Di Bisceglie AM et al. Combination of interferon and ribavirin in chronic hepatitis C: re-treatment of non-responders to interferon. *Hepatology*. 2001; 33:704-707.
17. Reichard O et al. Randomized, double-blind, placebo-controlled trial of interferon alfa-2b with and without ribavirin for chronic hepatitis C. *Lancet*. 1998; 351:83-87.
18. Chalasani N et al. Peginterferon alfa-2a for hepatitis C after liver transplantation: two randomized, controlled trials. *Hepatology*. 2005; 41:289-298.
19. Sharma P and Lok A. Viral Hepatitis and Liver Transplantation. *Semin Liver Dis* 2006; 26:285-297.
20. Wang CS, Ko HH, Yoshida EM et al. Interferon-Based Combination Anti-Viral Therapy for Hepatitis C Virus After Liver Transplantation: A Review and Quantitative Analysis. *American Journal of Transplantation* 2006;6(7):1586-1599.
21. Kuo A and Terrault N A. Management of Hepatitis C in Liver Transplant Recipients. *American Journal of Transplantation* 2006;6(3):449-58.
22. Afdhal NH, Levine R, Brown R et al. Colchicine versus peg-interferon alfa 2b long-term therapy: Results of the 4 year COPILOT Trial [abstract]. 43rd Annual Meeting of the European Association for the Study of the Liver (EASL 2008). Milan, Italy. April 23-27, 2008.
23. Jensen D, Freilich B, Andreone P et al. Pegylated interferon alfa-2a (40KD) plus ribavirin (RBV) in prior non-responders to pegylated interferon alfa-2b (12KD)/RBV: Final efficacy and safety outcomes of the REPEAT study. 58th Annual Meeting of the AASLD, Boston, MA, November 2-6, 2007.
24. Bacon B, Regev A, Ghalib R et al. Use of daily interferon alfacon-1 (Infergen) plus ribavirin in patients infected with hepatitis C virus who are nonresponders to previous pegylated interferon plus ribavirin therapy: 24-week and end of treatment data from the DIRECT Trial [abstract]. Poster No. LB18. Presented at the 57th Annual Meeting of the American Association for the Study of Liver Diseases, Boston, MA, October 27-31, 2006.
25. Fartoux L, Degos F, Trépo C et al. Effect of prolonged interferon therapy on the outcome of hepatitis C virus-related cirrhosis: A randomized trial. *Clin Gastroenterol Hepatol*. 2007; 5(4):502-507.
26. Sulkowski M, Lawitz E, Shiffman ML et al. Final results of the IDEAL (Individualized Dosing Efficacy Versus Flat Dosing to Assess Optimal Pegylated Interferon Therapy) phase IIIb study [abstract]. 43rd Annual Meeting of the European Association for the Study of the Liver (EASL 2008). Milan, Italy. April 23-27, 2008.
27. Di Bisceglie AM, Shiffman ML, Everson GT et al.; HALT-C Trial Investigators. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. *N Engl J Med*. 2008;359(23):2429-2441.
28. Marcellin P, Craxi A, Brandao-Mello CE et al. A 72-week treatment duration with peginterferon alfa-2a (40KD) (Pegasys) plus ribavirin (Copegus) has a favorable risk:benefit ratio in non-responders to pegylated interferon alfa-2b (12KD) plus ribavirin: findings of the multinational REPEAT study. Poster presented at the 59th Annual Meeting of the American Association for the Study of Liver Disease (AASLD). San Francisco, CA. October 31 – November 4, 2008.
29. Rumi M, Aghemo A, Prati G et al. Randomized study comparing peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin in naive patients with chronic hepatitis C: final results of the Milan Safety Tolerability (MIST) Study. Presented at



the 59th Annual Meeting of the American Association for the Study of Liver Disease (AASLD). San Francisco, CA. October 31 – November 4, 2008.

30. Ascione A, DeLuca M, Tartaglione MT et al. Peginterferon alpha-2<sup>o</sup> plus ribavirin versus peginterferon alpha-2b plus ribavirin in naive patients with chronic hepatitis C virus infection: results of a prospective randomized trial. Presented at the 43rd Annual Meeting of the European Association for the Study of the Liver (EASL 2008). Milan, Italy. April 23-27, 2008.
31. Poynard T, Schiff E, Terg R et al. Sustained viral response (SVR) is dependent on baseline characteristics in the retreatment of previous alfa interferon/ribavirin (I/R) nonresponders (NR): final results from the EPIC3 program [abstract]. *J Hepatol.* 2008;48(Suppl 2):S308.
32. Poynard T, Schiff E, Terg R et al. Platelet count predicts sustained viral response (SVR) in the re-treatment of previous interferon/ribavirin non-responders (NR): results from the EPIC3 program [abstract]. *J Hepatol.* 2008;48(Suppl 2):S308.
33. Baker RD, Dee D, Baker SS. Response to pegylated interferon alpha-2b and ribavirin in children with chronic hepatitis C. *J Clin Gastroenterol.* 2007 Jan;41(1):111-4.
34. AASLD, IDSA. Recommendations for Testing, Managing, and Treating Hepatitis C. Web publication, available at <http://www.hcvguidelines.org>. Accessed June 13, 2024.
35. Jacobson I, Gordon S, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013;368:1867-77.
36. Lawitz E, Mangia A, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013;368:1878-87.
37. Zeuzem S, Dusheiko G, et al. Sofosbuvir + ribavirin for 12 or 24 weeks for patients with HCV genotype 2 or 3: the VALENCE trial. Presented at: 64th Annual Meeting of the American Association of the Study of Liver Diseases; Nov 1-5, 2013; Washington, DC. Available at: [http://www.natap.org/2013/AASLD/AASLD\\_15.htm](http://www.natap.org/2013/AASLD/AASLD_15.htm) Accessed June 13, 2024.
38. Sulkowski M, Rodriguez-Torres M, et al. All-oral therapy with sofosbuvir plus ribavirin for the treatment of HCV Genotype 1, 2, and 3 infection in patients co-infected with HIV (PHOTON-1). Presented at: 64th Annual Meeting of the American Association of the Study of Liver Diseases; Nov 1-5, 2013; Washington, DC. Available at: [http://www.natap.org/2013/AASLD/AASLD\\_34.htm](http://www.natap.org/2013/AASLD/AASLD_34.htm) Accessed June 13, 2024.
39. Nakano, T; Lau, GM; Lau, GM et al. (December 2011). "An updated analysis of hepatitis C virus genotypes and subtypes based on the complete coding region". *Liver Int.* 32 (2): 339–45.
40. Charlton M, Gane E, Mannus MP, et al. Sofosbuvir and ribavirin for the treatment of established recurrent hepatitis c infection after liver transplantation: a prospective, multicenter study. Oral presentation at the Liver Meeting: The 64th Annual Meeting of the American Association for the Study of Liver Disease; November 1-5, 2013. Washington, DC. Oral presentation LB-2. Available through SOVALDI dossier.
41. Fred Poordad MPM, Patrick Marcellin, Evaldo Stanislaw Affonso de Araujo, Maria Buti, Yves Horsmans, Ewa Janczewska, Federico Villamil, Monika Peeters, Oliver Lenz, Sivi Ouwerkerk-Mahadevan, Ronald Kalmeijer, Maria Beumont-Mauviel. Simeprevir (Tmc435) With Peginterferon/Ribavirin for Treatment of Chronic HCV Genotype-1 Infection in Treatment-NaïVE Patients: Results From Quest-2, a Phase III Trial (Presentation Number 869a) *Digestive Disease Week.* Orlando, Florida, USA2013.
42. Ira M. Jacobson GJD, Graham Foster, Michael W. Fried, Monica N. Radu, Vladimir V. Rafalskiy, Larysa Moroz, Antonio Craxi, Monika Peeters, Oliver Lenz, Sivi Ouwerkerk-Mahadevan, Ronald Kalmeijer, Maria Beumont-Mauviel. Simeprevir (Tmc435) With Peginterferon/Ribavirin for Chronic HCV Genotype-1 Infection in Treatment-NaïVE Patients: Results from Quest-1, a Phase III Trial (Presentation Number Sa2072). *Digestive Disease Week.* Orlando, Florida, USA2013.
43. Eric Lawitz XF, Stefan Zeuzem, Edward Gane, Jean-Pierre Bronowicki, Pietro Andreone, Andrzej Horban, Ashley Brown, Monika Peeters, Oliver Lenz, Sivi Ouwerkerk-Mahadevan, Ronald Kalmeijer, Maria Beumont-Mauviel. Simeprevir (Tmc435) With Peginterferon/Ribavirin for Treatment of Chronic HCV Genotype 1 Infection in Patients WHO Relapsed After Previous Interferon-Based Therapy: Results From Promise, a Phase III Trial (Presentation Number 569b). *Digestive Disease Week.* Orlando, Florida, USA2013.
44. Eric Lawitz RG, Maribel Rodriguez-Torres, Zobair M. Younossi, Ana Corregidor, Ira M. Jacobson, Kathleen Callewaert, William T. Symonds, Gaston Picchio, Karen Lindsay. Svr4 Results of a Once Daily Regimen of Simeprevir (Tmc435) Plus Sofosbuvir (Gs-





7977) With or Without Ribavirin (RBV) in HCV GT 1 Null Responders (COSMOS Study) (Presentation Sa2073). Digestive Disease Week. Orlando, Florida, USA2013.

45. Dieterich D RJ, Orkin C, et al. Simeprevir with pegylated interferon/ribavirin in patients co-infected with chronic hepatitis C virus and HIV-1: week-24 interim analysis of the TMC435-C212 study (Abstract 154LB). Paper presented at: Conference on Retroviruses and Opportunistic Infections 2013; Atlanta, GA, USA.
46. Harvoni (ledipasvir and sofosbuvir) [prescribing information]. Gilead Sciences, Inc. Foster City, CA, Revised March 2020.
47. Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. *Gastroenterology*. 2014 Aug;147(2):359-365. (PEARL-II).
48. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med*. 2014;370(17):1594-1603. (SAPPHIRE-I).
49. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med*. 2014;370(21):1983-1992. (PEARL-III/IV).
50. Kwo PY, Mantry PS, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med*. 2014;371(25):2375-2382. (CORAL-I).
51. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med*. 2014;370(21):1973-1982. (TURQUOISE-II)
52. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med*. 2014;370(17):1604-1614. (SAPPHIRE-II)
53. American Liver Foundation. Your Liver: Liver Disease Information: Non-Alcoholic Fatty Liver Disease. Last updated January, 2015, Available at: <http://www.liverfoundation.org/abouttheliver/info/naflid> Accessed June 13, 2024.
54. Zepatier (elbasvir and grazoprevir) [prescribing information]. Merck&Co.; Whitehouse Station, NJ. Revised May 2022.
55. Epclusa (sofosbuvir/velpatasvir) [prescribing information]. Gilead Sciences, Inc.; Foster City, CA. Revised April 2022.
56. Vosevi (sofosbuvir/velpatasvir/voxilaprevir) [prescribing information]. Gilead Sciences, Inc.; Foster City, CA. Revised November, 2019.
57. Mavyret (glecaprevir/pibrentasvir) [prescribing information]. AbbVie Inc.; North Chicago, IL. Revised October 2023.
58. Pegasys (peginterferon alfa-2a) [prescribing information]. Genentech, Inc.; South San Francisco, CA. Revised March 2021.
59. PegIntron (peginterferon alfa-2b) [prescribing information]. Merck & Co., Inc., Whitehouse Station, NJ. Revised August 2019.
60. Sovaldi (sofosbuvir) [prescribing information]. Gilead Sciences, Inc., Foster City, CA. Revised March 2020.
61. Harvoni (ledipasvir-sofosbuvir) [prescribing information]. Gilead Sciences, Inc., Foster City, CA. Revised March 2020.

## History

Date	Comments
11/11/05	Add to Prescription Drug Section - New policy, held for notification—originally scheduled to publish 4/1/06; due to system logistics publication moved to 5/1/06. P&T reviewed 1/27/06 minor changes incorporated.



Date	Comments
06/16/06	Update Scope and Disclaimer - No other changes.
11/14/06	Replace Policy - Policy reviewed by Pharmacy and Therapeutics Committee on September 26, 2006; recommended for adoption with no changes to policy statement.
01/09/06	Replace Policy - Policy updated with references and addition of medically necessary policy statement for treatment of liver transplant patients. Policy reviewed by P&T 11/28/06.
02/12/08	Replace Policy - Policy updated with literature search; no change to the policy statement. Reviewed by Pharmacy and Therapeutics Committee on January 22, 2008; recommended for adoption with no changes to policy statement.
05/12/09	Replace Policy - Policy updated with literature search. Policy statements re-written for clarification. References added.
07/29/09	Update Benefit Application - No other changes.
05/11/10	Replace Policy - Policy statement revised to indicate initiation of greater than 2 courses of retreatment with pegylated interferon plus ribavirin per year for relapse or non-response must be reviewed and approved by a Medical Director on a case-by-case basis; and slow responder patients with a $\geq 2$ log decrease in hepatitis C viral load after 12 weeks of therapy, an additional 12 weeks of combination treatment may be reauthorized. Patients in this subpopulation who have undetectable HCV-RNA after 24 weeks of therapy may be reauthorized for up to an additional 48 weeks of treatment with a pegylated interferon plus ribavirin (for up to a 72-week course of therapy). Reviewed and recommended by P&T in March 2010.
05/10/11	Replace Policy - Policy updated with literature review; no change in policy statement.
10/24/11	Coding update: HCPCS S0146 removed; S0148 added.
06/12/12	Replace policy. Updated to include Hepatitis C protease inhibitor criteria. Deleting review requirement for interferons in Hepatitis B, as this use is very infrequent.
10/11/12	Minor Update – Medco is now Express Scripts.
07/08/13	Minor Update – Clarification was added to the policy that it is managed through the member’s pharmacy benefit; this is now listed in the header and within the coding section.
12/09/13	Replace policy. Policy updated with review; no change in policy statement. CPT codes removed from the policy; this policy is managed through the pharmacy benefit.
04/14/14	Annual review. Policy updated with Sovaldi (sofosbuvir) as medically necessary as combination therapy for the listed FDA-approved indications of chronic hepatitis C for off-label indications when all criteria are met; it is investigational for all other indications. Olysio (simeprevir) is added as medically necessary as combination therapy for the FDA-approved indication for chronic hepatitis C genotype 1; all other uses are considered investigational. ICD-9 diagnosis codes removed from policy; they are not utilized in adjudication.



Date	Comments
09/08/14	Interim review. Policy section updated with new direct-acting antiviral agents (DAA) as medically necessary treatment regimens for chronic hepatitis C when criteria are met; guidelines for prioritization of patients and expanded treatment information for genotypes 3-5 added (previously only genotypes 1 and 2 were addressed). This update reflects combined AASLD and IDSA guidelines for the treatment of chronic hepatitis C.
11/10/14	Interim review. Policy updated with literature search and information on FDA-approval of the new ledipasvir/sofosbuvir product (Harvoni) to treat all genotype 1 patients on October 10, 2014. Additionally, the FDA recently approved the combination use of simeprevir (Olysio) and sofosbuvir (Sovaldi) to treat Hepatitis C; however, there is no evidence of improved patient outcomes versus use of Harvoni, and this therapy regimen is considered not medically necessary.
12/22/14	Interim update. Clarifying wording added to the not medically necessary policy statement regarding combination therapy of simeprevir (Olysio) and sofosbuvir (Sovaldi): "since an equally or more effective alternative, ledipasvir/sofosbuvir (Harvoni), is available at a much lower cost." Regimen tables updated to align with policy statements: SOF (Sovaldi) / SMV (Olysio) ± RBV removed as a regimen to treat either treatment naïve or treatment resistant patients with Genotype 1; this regimen has been replaced with Harvoni.
01/30/15	Annual review. Policy updated with addition of exceptions to specific treatment regimen guidelines relative to Viekira Pak within the Policy section. References 59-64 added.
04/14/15	Interim Review. Policy updated for treatment naïve patients with addition of Harvoni for genotype 4 and 6; addition of Viekira Pak for genotype 1 and 4; addition of Sovaldi /Olysio for genotype 1. Policy updated for treatment experienced patients with addition of Harvoni for genotype 4 and 6; addition of Viekira Pak for genotype 4; Sovaldi/Olysio for genotype 1; addition of Sovaldi/RBV for genotype 4. Multiple regimens for each genotype in the "alternative therapy" column have been removed as those are no longer recommended by the AASLD/IDSA guidelines. All data used have been taken from the AASLD/IDSA guidelines. Medical necessity criterion for proteinuria levels delineated to >2 grams urinary protein/24hours related to cryoglobulinemia. "Exceptions" section updated with the application to genotypes 1 and 4 only; genotype 6 removed. HCPCS codes J9213, J9214, S0145 and S0148 removed; these are not reviewed.
08/11/15	Interim Update: Added one more prioritization criteria to the list, as well as a brief description of NASH and NAFLD to the discussion section, Added two new agents: Technivie and Daklinza.
09/08/15	Interim update. Policy section addition to address re-treatment criteria after all DAA regimen.
11/10/15	Interim Update. Added type I diabetes as a prioritization criteria to the section "Prioritizing Patients for Treatment for Chronic Hepatitis C."



Date	Comments
12/08/15	Interim update. Medical necessity prioritization criteria removed. Charts for initial and retreatment revised to remain consistent with AASLD guidelines and for clarity; intent is unchanged.
01/08/16	Clarified that Viekira Pak is approved for genotype 1 in Exceptions explanation.
03/08/16	Interim update. Addition of one new agent Zepatier, and its related criteria and clinical summary.
05/01/16	Annual Review, approved April 12, 2016. Revision of the policy language; removal of the drug tables.
06/14/16	Interim Update. Clarification of the Harvoni step requirement, and removal of outdated information.
06/30/16	Interim Update: Inclusion of the criteria for a brand new agent named Epclusa (sofosbuvir/velpatasvir). Currently has the same status as Harvoni. Status is subject to change.
07/08/16	Minor formatting updates for clarity.
09/01/16	Interim Update, approved August 9, 2016. Inclusion of an updated version of Viekira Pak (Viekira XR).
01/01/17	Interim Review, approved December 13, 2016. Step therapy criteria requiring the use of Harvoni before Epclusa can be approved has been added to the Exceptions section of the policy.
04/21/17	Policy moved into new format; no change to policy statements.
09/15/17	Annual Review, approved September 12, 2017, effective September 15, 2017. Policy updated to reflect new criteria for preferred DAA agents, adding Mavyret and Vosevi as preferred agents replacing Harvoni and Epclusa where indicated. Update reflecting current guideline recommendations.
09/25/17	Interim Review, approved September 22, 2017, effective September 25, 2017. Modified step therapy criteria. Harvoni re-incorporated into policy as a preferred treatment agent; length of therapy information included.
12/01/18	Annual Review, approved November 21, 2018. Reviewed changes to AASLD/IDSA guidelines. No changes required. Remove HCPCS code J8499.
08/01/19	Interim Review, approved July 25, 2019. Updated criteria for Mavyret. Documented Epclusa and Vosevi are FDA-approved for adult patients.
10/01/19	Annual Review, approved September 5, 2019. Added prior authorization for Pegasys (peginterferon alfa-2a) and PegIntron (peginterferon alfa-2b).
02/01/20	Interim Review, approved January 9, 2020. Modified treatment duration of Mavyret treatment-naïve patients to 8 weeks.
01/01/21	Annual Review, approved December 17, 2020. Updated Epclusa (sofosbuvir/velpatasvir) coverage criteria to include pediatric patients 6 years of age



Date	Comments
	and older or weighing at least 17 kg. Updated Harvoni (ledipasvir/ sofosbuvir) coverage criteria to include pediatric patients 3 years of age and older.
08/01/21	Annual Review, approved July 9, 2021. Updated Mavyret (glecaprevir/ pibrentasvir) to include all pediatric patients 3 years of age and older and removed requirement patients weigh at least 45 kg. Updated Eplclusa (sofosbuvir/velpatasvir) to include all pediatric patients 3 years of age and older and removed requirement patients weigh at least 17 kg. Updated Harvoni (ledipasvir/sofosbuvir) criteria to include length of therapy based on HCV genotype and patient population. Updated Vosevi (sofosbuvir, velpatasvir, and voxilaprevir) criteria to document length of therapy is 12 weeks for all approved indications.
11/01/22	Annual Review, approved October 24, 2022. No changes to the policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
07/01/23	Annual Review, approved June 26, 2023. No changes to the policy statements.
11/01/23	Interim Review, approved October 23, 2023. Moved Pegasys (peginterferon alfa-2a) policy criteria for the treatment of chronic hepatitis B from this policy to Policy 5.01.636 Chronic Hepatitis B Antiviral Therapy. Added 5.01.636 Chronic Hepatitis B Antiviral Therapy to Related Policy section.
08/01/24	Annual Review, approved July 8, 2024. No changes to the policy statements.
01/01/25	Interim Review, approved December 10, 2024. Added FDA approved uses for brand sofosbuvir-velpatasvir, brand ledipasvir-sofosbuvir, Sovaldi (sofosbuvir) and Zepatier (elbasvir-grazoprevir). New policy section with headers added for Section 2 (individual/small group/student ISHIP Metallic formulary plans) with hyperlinks to aid navigation. Added separate coverage criteria for Metallic (individual/small group/student ISHIP plans) formulary members for the following drugs: Eplclusa, brand ledipasvir-sofosbuvir, Harvoni, Mavyret, brand sofosbuvir-velpatasvir, Sovaldi, Vosevi, and Zepatier. For Section 1 (non-Metallic formulary plans and plans with no pharmacy benefit coverage), clarified that Sovaldi (sofosbuvir) and Vosevi (sofosbuvir-velpatasvir-voxilaprevir) are preferred products. For Section 1, indicated that Zepatier (elbasvir-grazoprevir) may be considered medically necessary for the treatment of DAA treatment experienced individuals according to the current AASLD and IDSA guideline recommendations. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2025 Premera All Rights Reserved.



**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

