

California Department of Health Care Services Utilization and Treatment Policy for Simeprevir and Sofosbuvir in the Management of Hepatitis C

Introduction

This policy was developed by the California Department of Health Care Services (DHCS) based on a review of the medical literature, the most recent guidelines and reports published by the American Association for the Study of Liver Diseases (AASLD), Infectious Diseases Society of America (ISDA) http://www.hcvguidelines.org/sites/default/files/full_report.pdf, European Association for the Study of the Liver (EASL) <http://files.easl.eu/easl-recommendations-on-treatment-of-hepatitis-C.pdf>, California Technology Assessment Forum/Institute for Clinical and Economic Review (ICER) <http://www.icer-review.org/california-technology-assessment-forum-ctaf-issues-final-report-and-action-guides-on-new-treatments-for-hepatitis-c/>, World Health Organization (WHO) http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1, federal Department of Veterans Affairs (VA), <http://www.hepatitis.va.gov/provider/guidelines/2014hcv/index.asp> and recommendations from experts in the management of hepatitis C virus (HCV). The treatment of HCV is rapidly evolving. Accordingly, this policy will be revised as new information becomes available.

Utilization and Treatment Policy

1. Treatment Considerations and Choice of Regimen for HCV-Monoinfected and HIV/HCV Co-infected Patients.

This utilization and treatment policy is based on the Veterans Affairs April 2014 guidelines entitled, Chronic Hepatitis C Virus Infection (HCV): Treatment Considerations (VA guidelines). Please see DHCS summary table and summary figure for detailed algorithmic information.

1.1. For genotypes 1,2, and 3, patients with mild liver disease (equivalent to METAVIR F0-2), except for those with serious extra-hepatic manifestations or post-liver transplant (see Section 5), are not eligible for sofosbuvir- or simeprevir-based regimens.

1.2 Non-FDA approved therapy will only be approved by DHCS for coverage if all criteria for coverage of investigational services are met (Title 22 § 51303).

Please see Section 11 of this document for the specific investigational criteria. Specific examples include, but are not limited to:

- 1.2.1 Genotype 1, treatment-naïve, not interferon (IFN) eligible and cirrhotic patients, the combination of sofosbuvir and simeprevir +/- ribavirin is not FDA approved.
- 1.2.2 Genotype 2, treatment experienced, interferon-eligible patients, the combination of sofosbuvir and interferon/ribavirin is not FDA approved.
- 1.2.3. Genotype 3, cirrhotic, interferon-eligible patients, sofosbuvir and interferon/ribavirin is not FDA approved.
- 1.2.4. For post-liver transplants sofosbuvir and interferon and/or ribavirin is not FDA approved.

2. IFN-Intolerant/Ineligible Criteria: Patients who are interferon ineligible must meet one or more of the following criteria:

- 2.1. Platelet count <100,000/mm³
- 2.2. Decompensated liver cirrhosis (Child-Turcotte-Pugh (CTP) Class B or C, CTP score greater than or equal to 7, albumin less than 3.5)
- 2.3. Severe mental health conditions (including, but not limited to psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder) that may be exacerbated by interferon or respond poorly to medical therapy.
- 2.4. Autoimmune diseases that may be exacerbated by interferon-mediated immune modulations.
- 2.5. Inability to complete prior treatment course due to documented interferon-related adverse effects.
- 2.6. A history of preexisting cardiac disease

3. Identifying Treatment Candidates Based on Liver Disease Stage

3.1. For consideration of treatment with sofosbuvir and/or simeprevir as part of a Hepatitis C treatment regimen, all patients must have a documented METAVIR score of F3 (advanced fibrosis) or F4 (cirrhosis) on liver biopsy OR strong clinical suspicion for advanced fibrosis/compensated cirrhosis based on the following criteria:

- 3.1.1. Clinical findings/Abdominal findings: Physical exam findings (palpable left lobe, splenomegaly, palmar erythema) AND Low platelet count (<100,000/mm³ AND abdominal imaging findings. Pertinent

abdominal imaging findings include Surface abnormalities (e.g. nodularity, and left lobe/caudate lobe hypertrophy) are suggestive of cirrhosis. Features of portal hypertension (e.g., splenomegaly (>12cm), recanalization of umbilical vein, collaterals) and ascites are also suggestive of cirrhosis.

3.1.2. Serum markers of advanced fibrosis/cirrhosis: Either APRI score of >1.5 (associated with METAVIR score F3) , FIB-4 >3.25 (associated with METAVIR F3-F4), or Fibrosure/Fibrotest >0.58.

3.1.3. Non-invasive assessment of liver fibrosis: Either Fibroscan >9.5 kilopascals, ARFI >1.75 meters/second, or magnetic resonance elastography (MRE) >6.47 kilopascals.

3.2. Documentation: Documentation of eligibility for treatment must be submitted with Treatment Authorization Request (TAR).

4. Laboratory monitoring/Assessment of HCV RNA

4.1. All patients receiving a sofosbuvir-based regimen or simeprevir-based regimen must have HCV RNA assessed at baseline.

4.2. Sofosbuvir-based regimens: Patients receiving a sofosbuvir-based regimen must have HCV RNA assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any time point thereafter, reassess HCV RNA in 2 weeks. If HCV RNA increases (i.e., >1 log₁₀ IU/mL from nadir) at any time point or if the 8-week HCV RNA is detectable, discontinuation of all treatment must be strongly considered.

4.3. Simeprevir-based regimens: Patients receiving a simeprevir-peginterferon-ribavirin regimen must have HCV RNA levels assessed at weeks 4, 12, and 24 weeks; if the HCV RNA is detectable: at any of these time points, all treatment should be discontinued.

4.4. After completion of treatment: HCV RNA levels are required at 12 weeks after the end of treatment to determine if SVR was achieved.

5. Groups with Special Considerations for Therapy

5.1. HCV/HIV Coinfection

5.1.1. Risk versus benefits of treatment must be carefully considered and consultation with an infectious disease (ID)/HIV specialist is strongly recommended.

5.1.2. Patients with uncontrolled HIV infection and advanced immunosuppression should begin HIV antiretrovirals before considering therapy for HCV.

5.1.3 Optimal candidates for HCV treatment are patients who have been on a stable regimen for HIV with a suppressed HIV viral load for at least 8 weeks and have an absolute CD4 count >200 cells/mm.

5.2. Renal insufficiency

5.2.1. Sofosbuvir must not be used if creatinine clearance (CrCl) is <30 mL/min or in end-stage renal disease. Simeprevir has not been studied in HCV-infected patients with CrCl<30 mL/min. However, no dosage adjustment is needed.

5.3. Pre/post-liver transplant

5.3.1. Post-liver transplant patients may be considered for therapy regardless of stage. There are a number of relevant clinical issues regarding pre/post liver transplant patients including modifications to duration of treatment. Thus, close collaboration with a transplant center is required. Please refer to VA guidelines for specific details.

5.4. Solid organ transplant (other than liver)

5.4.1. Patients post-other solid organ transplant (e.g., kidney, heart, lung) must be discussed with transplant center to assess post-transplant treatment candidate selection and type of regimen.

5.4.2. Sofosbuvir has not been studied in non-liver transplant recipients

5.5. With respect to eligibility for treatment, extra-hepatic manifestations include: Leukocytoclastic vasculitis, clinical evidence of symptomatic cryoglobulinemia and membranoproliferative glomerulonephritis. Patients with mild liver disease (equivalent to F0-F2) AND extra-hepatic manifestations should be considered for treatment. See summary figure and summary table for details.

5.6. Hepatocellular carcinoma (HCC): Patients with HCV and HCC should be considered for treatment. See summary figure and summary table for details.

5.7. Decompensated cirrhosis: Patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) must be referred to a physician with expertise in that condition (ideally in a liver transplant center).

5.8. Cirrhosis (compensated or decompensated): The exclusion of HCC based on imaging within the past 6 months must be documented in patients with compensated or decompensated cirrhosis.

6. Eligibility Criteria

6.1. Age 18 years of age or older

6.2. Substance Use

6.2.1. All patients should be evaluated for current alcohol and other substance abuse, with validated screening instruments such as AUDIT or AUDIT C. All patients considered for treatment with simeprevir or sofosbuvir must have urine toxicology screen at baseline.

6.2.2. The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once a month), and/or active injection drug use and/or other illicit drug use as documented with a positive urine toxicology screen requires referral to treatment of substance use disorder (preferably to an addiction treatment specialist) before HCV treatment initiation. Patients with a substance abuse disorder must be actively participating in treatment for the disorder or be abstinent for 6 months prior to the initiation of HCV treatment.

6.2.3. If a clinician feels that a patient's substance use will jeopardize adherence, it is reasonable to delay therapy until the patient is stabilized.

6.3. Mental Health Considerations

6.3.1. Patients must be screened for depression using PHQ-2, PHQ-9 or other screening tool prior to initiation of therapy. If positive, patient must be adequately and appropriately treated prior to initiation of therapy.

6.3.2. HCV therapy must be considered on a case-by-case basis in patients with severe mental health conditions (including, but not limited to: psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder) as documented by a psychiatric evaluation, and actively engaged in mental health treatment.

6.4. Screening Criteria

6.4.1. Patient must be screened and or/vaccinated for Hepatitis A and Hepatitis B if not infected or exposed, and screened for HIV within 30 days of treatment initiation, with appropriate laboratory evidence. If a patient

needs to be vaccinated, the vaccination series must be started prior to treatment.

6.4.2. Patients with Genotype 1a must be screened and negative for the NS3 Q80K polymorphism at baseline before initiation of a simeprevir + ribavirin/interferon regimen.

7. Patient exclusion criteria

7.1. Pregnancy status: Use of simeprevir or sofosbuvir in combination with ribavirin is contraindicated in pregnant women and in male partners of women who are pregnant.

7.1.1. When sofosbuvir (pregnancy class B) or simeprevir (pregnancy class C) is used in combination with ribavirin (pregnancy class X) it must NOT be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy with ribavirin.

7.1.2. Effective and reliable contraception is required during ribavirin therapy and for at least 6 months after therapy for women in whom there is a possibility of getting pregnant.

7.1.3. Routine monthly pregnancy tests must be performed during and 6 months after treatment with ribavirin is complete or terminated.

7.2. Assessment of Likelihood of Treatment Adherence

7.2.1. Caution must be exercised with patients who have a history of treatment failure with prior Hepatitis C treatment due to non-adherence.

7.2.2. Patient must understand potential risks and benefit of HCV therapy, as well as the potential for resistance and failed therapy if medication is not taken as prescribed.

7.3. Genotypes 4,5 or 6: There is insufficient evidence of benefit in the use of simeprevir or sofosbuvir in patients with genotype 4,5 or 6. Therefore, patients with genotype 4, 5 or 6 will be considered on a case-by-case basis.

8. Provider Inclusion Criteria

8.1. Medications are advised to be prescribed by or in consultation with a provider who has extensive experience treating Hepatitis C.

9. Criteria for Reauthorization/Continuation of Therapy

- 9.1. Initial authorization criteria have been met, and
- 9.2. Lost medications will not be replaced and may result in denial of treatment authorization. Replacement of stolen medications will require documentation and will be adjudicated on a case-by-case basis.
- 9.3. Evidence of lack of adherence may result in denial of treatment reauthorization.
- 9.4. Missed medical and lab appointments may result in denial of treatment authorization.

10. Quantity Limits

- 10.1. Initial treatment shall be approved for 8 weeks.
- 10.2. An 8 week prescription of simpeprevir or sofosbuvir will be dispensed two weeks at a time. It is not necessary to dispense sofosbuvir or simeprevir in their original containers.
- 10.3. Reauthorization requests are contingent upon submission of required laboratory data (see Section 4). A 14-day supply may be authorized to minimize treatment interruption pending laboratory results.

11. Criteria for coverage of Investigational Services (Title 22 § 51303)

- 11.1. Investigational services are not covered except when it is clearly documented that all of the following apply:
 - 11.1.1. Conventional therapy will not adequately treat the intended patient's condition;
 - 11.1.2. Conventional therapy will not prevent progressive disability or premature death;
 - 11.1.3. The provider of the proposed service has a record of safety and success with it equivalent or superior to that of other providers of the investigational service;

11.1.4. The investigational service is the lowest cost item or service that meets the patient's medical needs and is less costly than all conventional alternatives;

11.1.5. The service is not being performed as a part of a research study protocol;

11.1.6. There is a reasonable expectation that the investigational service will significantly prolong the intended patient's life or will maintain or restore a range of physical and social function suited to activities of daily living.

11.2. All investigational services require prior authorization. Payment will not be authorized for investigational services that do not meet the above criteria or for associated inpatient care when a beneficiary needs to be in the hospital primarily because she/he is receiving such non-approved investigational services.

12. Drug-drug interactions:

12.1. Sofosbuvir is not metabolized by the cytochrome P450 system of enzymes but is a substrate of P-glycoprotein (P-gp); P-gp inducers may decrease sofosbuvir plasma concentrations. Therefore, sofosbuvir must not be co-administered with any of the following: St. John's Wort, anticonvulsants (e.g. carbamazepine, phenytoin, phenobarbital, oxcarbazepine), antimycobacterials (e.g., rifabutin, rifampin, rifapentine), and tipranavir/ritonavir.

12.2. Simeprevir is metabolized by the CYP enzyme, CYP3A; coadministration with moderate or strong inducers or inhibitors of CYP3A is not recommended as this may decrease or increase simeprevir concentrations, respectively.

Simeprevir should not be coadministered with any of the following: milk thistle, St. John's wort, HIV protease inhibitors (with or without ritonavir), efavirenz, etravirine, nevirapine, antiretroviral agents containing cobicistat, antimycobacterials (e.g., rifabutin, rifampin, rifapentine), macrolides, azole antifungals, ketolides, dexamethasone, anticonvulsants (e.g. carbamazepine, phenytoin, phenobarbital, oxcarbazepine).