



Clinical Criteria for Hepatitis C (HCV) Therapy

Diagnosis

- Must have chronic hepatitis C, genotype and sub-genotype specified to determine the length of therapy;
- Liver biopsy or other accepted test demonstrating liver fibrosis corresponding to Metavir score of greater than or equal to 2;
- Consult performed and medication prescribed by a physician specializing in infectious disease or gastroenterology/hepatology.

Patient Treatment Plan

- Patient must have a treatment plan developed by the specialist.
- If patient is of childbearing age, she must utilize 2 forms of contraception.

Drug Therapy

- Must be in accordance to FDA approved indications.

Sofosbuvir (Sovaldi™)

RECOMMENDED REGIMENS AND TREATMENT DURATION FOR SOFOSBUVIR COMBINATION THERAPY IN HCV^{i,ii,iii,iv,v,vi}

HCV Genotype and Comorbidities	Treatment	Duration
Patients with genotype 1 or 4 HCV with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + peginterferon alfa + ribavirin	12 weeks
Patients with genotype 2 HCV with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + ribavirin	12 weeks
Patients with genotype 3 HCV with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + ribavirin	24 weeks
Patients with HCV/HIV-1 co-infection (genotype 1 or 4) with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + peginterferon alfa + ribavirin	12 weeks
Patients with genotype 1 HCV and interferon ineligible, with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + ribavirin	24 weeks
Patients with hepatocellular carcinoma awaiting liver transplantation	sofosbuvir + ribavirin	48 weeks (or until the time of liver transplantation; whichever occurs first)

Age Edit: Adult patients age ≥ 18 years old

Quantity Limit: One 400 mg tablet per day (28 tablets/28 days).

Length of Authorization:

Based on HCV subtype, Patient must be treatment naïve to sofosbuvir.

INITIAL: 8 weeks

REFILLS: Should be reauthorized for additional 8 week period at a time, depending on the treatment plan. The patient must receive refills within one week of completing the previous 28 day supply throughout treatment.

Monitoring of the Virological Response:**

- Rapid virologic response (RVR): ≥ 2 log reduction in HCV RNA for the baseline or undetectable after 4 weeks of therapy
- Early Virologic response (EVR): undetectable HCV RNA viral load at treatment week 12
- Sustained virologic response (SVR): HCV RNA negative 12 weeks after cessation of therapy

DISCONTINUATION OF DOSING

- It is unlikely that patients with inadequate on-treatment virologic response will achieve a sustained virologic response (SVR), therefore discontinuation of treatment is recommended in these patients.

Treatment Stopping Rules in Any Patient with Inadequate On-Treatment Virologic Response**

HCV RNA	Action
Treatment Week 4: ≥ 2 log reduction in HCV RNA from baseline	Discontinue sofosbuvir, peginterferon alfa and ribavirin
Treatment Week 12: greater than or equal to 25 IU/mL	Discontinue peginterferon alfa, ribavirin, and sofosbuvir (if applicable)
Treatment Week 24: greater than or equal to 25 IU/mL	Discontinue peginterferon alfa, ribavirin, and sofosbuvir (if applicable)

**** A FDA or AASLD recommendation for the discontinuation of treatment has not been released to date. Prescribers are encouraged to monitor HCV RNA to validate adherence to therapy/efficacy of therapy**

Interferon Alfa Ineligible Defined

- Intolerance to interferon alfa;
- Autoimmune hepatitis and other autoimmune disorders;
- Hypersensitivity to peginterferon alfa or any of its components;
- Decompensated hepatic disease;
- Documented history of depression or mood disorder, which are not stable on the current drug regimen;
- Platelet count $<75,000/\text{mm}^3$;
- A history of preexisting cardiac disease.

For documented diagnosis of HCV with *genotype 1 [Triple therapy]* Combination with peginterferon and ribavirin – Approval for 12 weeks

- Approve; **OR**
- Approve for HCV/HIV-1 co-infection; **OR**
- Approve for patients with compensated cirrhosis, including those with hepatocellular carcinoma
- Must have concurrent (or planning to start) therapy with ribavirin and peginterferon when starting sofosbuvir for a 12 week duration

For documented diagnosis of HCV with *genotype 1 [Dual therapy]* Combination with ribavirin – Approval for 24 weeks

- Patients **MUST** be interferon ineligible (document reason that patient is interferon ineligible)
- Approve; **OR**
- Approve for HCV/HIV-1 co-infection; **OR**
- Approve for patients with compensated cirrhosis, including those with hepatocellular carcinoma
- Must be used in combination with ribavirin therapy

For documented diagnosis of HCV with *genotype 2 [Dual therapy]* Combination with ribavirin – Approval for 12 weeks

- Approve; **OR**
- Approve for HCV/HIV-1 co-infection; **OR**
- Approve for patients with compensated cirrhosis, including those with hepatocellular carcinoma
- Must have concurrent (or planning to start) therapy with ribavirin when starting sofosbuvir for a 12 week duration

For documented diagnosis of HCV with genotype 3 [Dual therapy] Combination with ribavirin – Approval for 24 weeks

- Approve; **OR**
- *Approve* for HCV/HIV-1 co-infection; **OR**
- *Approve* for patients with compensated cirrhosis, including those with hepatocellular carcinoma
- Must have concurrent (or planning to start) therapy with ribavirin when starting sofosbuvir for a 24 week duration

For diagnosis of HCV with genotype 4 [Triple therapy] Combination with peginterferon and ribavirin – Approval for 12 weeks

- Approve; **OR**
- *Approve* for HCV/HIV-1 co-infection; **OR**
- *Approve* for patients with compensated cirrhosis, including those with hepatocellular carcinoma
- Must have concurrent (or planning to start) therapy with ribavirin and peginterferon when starting sofosbuvir for a 12 week duration

For diagnosis of hepatocellular carcinoma awaiting liver transplantation [Dual therapy] Combination with ribavirin – Approval for 48 weeks

- Sofosbuvir efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria **and** awaiting liver transplantation)
- Must have concurrent (or planning to start) therapy with ribavirin when starting sofosbuvir for a 48 week duration or until the time of liver transplantation, whichever occurs first.
- Milan criteria defined as:
 - the presence of a tumor 5 cm or less in diameter in subjects with single hepatocellular carcinoma; **AND**
 - no more than three tumor nodules, each 3 cm or less in diameter, in subjects with multiple tumors; **AND**
 - no extrahepatic manifestations of the cancer and no evidence of vascular invasion of the tumor

ADDITIONAL SOFOSBUVIR INFORMATION TO AID IN THE FINAL DECISION

- Remind all providers that HCV-RNA levels will need to be obtained at treatment week 4 for continuation of treatment

- Approve for 8 weeks of initial therapy to begin with in order to allow time for lab test results to be processed.
- Must have baseline HCV RNA level within 30 days of anticipated treatment start date
- Patient is not receiving concomitant therapy with a hepatitis protease inhibitor (e.g. telaprevir (Incivek), or boceprevir (Victrelis).
- Sofosbuvir combination treatment with ribavirin or peginterferon alfa/ribavirin is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant because of the risks for birth defects and fetal death associated with ribavirin.
- Patient does *not* have decompensated cirrhosis (which is defined as a Child-Pugh score greater than 6 [class B or C]).
- Patient does *not* have severe renal impairment (eGFR <30 mL/min/1.73m²) or end stage renal disease (ESRD) requiring hemodialysis.
- The safety and efficacy have not been established in post-liver transplant patients.
- Patient must be 6 months free of substance/alcohol/opioid dependence.
- There is insufficient data to recommend use in patients with HCV genotypes 5 or 6.
- For HIV-1 lab report documenting that patient has HIV-1; AND
 - CD4 count greater than 500 cells/mm³, if patient is not taking antiretroviral therapy; **OR**
 - CD4 count greater than 200 cells/mm³, if patient is virologically suppressed (e.g. HIV RNA < 200 copies/mL)

ⁱ Sovaldi [package insert]. Foster City, CA; Gilead, December 2013.

ⁱⁱ FDA Antiviral Drugs Advisory Committee Meeting, October 25, 2013; Background Package for NDA 204671 sofosbuvir (GS-7977).

ⁱⁱⁱ Sovaldi [package insert]. Foster City, CA; Gilead, December 2013.

^{iv} Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013; 368:1878-87. doi: 10.1056/NEJMoa1214853. Available at: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1214853>. Accessed January 2, 2014.

^v Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013;368:1867-77. doi: 10.1056/NEJMoa1214854. Available at: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1214854>. Accessed January 2, 2014.

^{vi} American Association for the Study of Liver Diseases Infectious Diseases Society of America: Recommendations for testing, managing and treating hepatitis C. Available at: <http://www.hcvguidelines.org/>. Accessed February 18, 2014.

Simeprevir (Olysio™)^{vi,vi}

Length of Authorization:

INITIAL: 8 weeks for all three agents

RENEWAL: Request week 4 labs for renewal (see below). If meet renewal criteria, then reauthorize an additional 4 weeks of therapy with all three agents for a total duration of 12 weeks.

Refills: The patient must receive refills within one week of completing the previous supply.

Quantity Limit: Simeprevir 150mg should have a quantity limit of 1 tablet per day for a total duration of 12 weeks.

Approval Criteria: Approve simeprevir initially for 8 weeks of therapy if ALL of the following are true:

- Prescriber must specialize in infectious disease or gastro-enterology/hepatology
- Diagnosis of hepatitis C virus (HCV) with genotype 1; **AND**
- Patient CANNOT have failed therapy with an oral protease inhibitor indicated for HCV (e.g., Incivek®, Victrelis®, or Olysio); **AND**
- Must have concurrent (or planning to start) therapy with ribavirin and peginterferon when starting simeprevir; **AND**
- Must be an adult patient age 18 and over; **AND**
- Patient has NOT had liver transplant; **AND**
- Patient is NOT infected with HCV genotype 1a containing the Q80K polymorphism; **AND**
- Patient is NOT co-infected with HCV/HIV

RENEWAL

After 8 weeks of therapy, approve simeprevir, peginterferon alfa and ribavirin for an additional 4 weeks of therapy if HCV-RNA shows a minimum 2 log reduction from baseline at treatment week 4

After 8 weeks of therapy, discontinue simeprevir, peginterferon alfa, and ribavirin if HCV-RNA does not show a 2 log or greater reduction from baseline at treatment week 4.

DISCONTINUATION OF DOSING

It is unlikely that patients with inadequate on-treatment virologic response will achieve a sustained virologic response (SVR), therefore discontinuation of treatment is recommended in these patients.

Treatment Stopping Rules in Any Patient with Inadequate On-Treatment Virologic Response

HCV RNA	Action
Treatment Week 4: ≥ 2 log reduction from baseline viral load	Discontinue simeprevir, peginterferon alfa and ribavirin
Treatment Week 12: greater than or equal to 25 IU/mL	Discontinue peginterferon alfa and ribavirin (treatment with simeprevir is complete at week 12)
Treatment Week 24: greater than or equal to 25 IU/mL	Discontinue peginterferon alfa and ribavirin

Additional information to aid in the final decision:

- Remind all providers that HCV-RNA viral levels will need to be obtained at treatment week 4 for continuation of treatment with simeprevir and week 12 for continuation of treatment with interferon and ribavirin.
- Approve for 8 weeks of initial therapy to begin with in order to allow time for lab test results to be processed.
- Patient must be 6 months free of substance/alcohol/opioid dependence, unless a patient has significant progression of disease state.
- Patient with confirmed diagnosis and history of depression or mood disorder, if stable on current medication than follow triple drug therapy regimen, otherwise use dual drug therapy regimen.

^{vi} Sovaldi [package insert]. Foster City, CA; Gilead, December 2013.

^{vi} FDA Antiviral Drugs Advisory Committee Meeting, October 25, 2013; Background Package for NDA 204671 sofosbuvir (GS-7977).

^{vi} Sovaldi [package insert]. Foster City, CA; Gilead, December 2013.

^{vi} Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med.* 2013; 368:1878-87. doi: 10.1056/NEJMoa1214853. Available at: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1214853>. Accessed January 2, 2014.

^{vi} Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med.* 2013;368:1867-77. doi: 10.1056/NEJMoa1214854. Available at: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1214854>. Accessed January 2, 2014.

^{vi} American Association for the Study of Liver Diseases Infectious Diseases Society of America: Recommendations for testing, managing and treating hepatitis C. Available at: <http://www.hcvguidelines.org/>. Accessed February 18, 2014.

^{vi} Olysio [package insert]. Janssen Therapeutics; Titusville, NJ. November 2013.

^{vi} American Association for the Study of Liver Diseases Infectious Diseases Society of America: Recommendations for testing, managing and treating hepatitis C. Available at: <http://www.hcvguidelines.org/>. Accessed February 18, 2014.

Retreatment Guidelines

HCV Genotype	Treatment	Duration of Total Therapy
Recommended Treatment genotype 1		
Patients (with previous HCV protease inhibitor therapy) with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + peginterferon alfa + ribavirin	12 to 24 weeks
Alternative Regimen genotype 1		
Patients (interferon eligible) (with or without previous HCV protease inhibitor therapy) with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + peginterferon alfa + ribavirin	12 to 24 weeks
Patients (interferon ineligible) (with or without previous HCV protease inhibitor therapy) with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + ribavirin	24 weeks
Patients (without previous HCV protease inhibitor therapy) with or without compensated cirrhosis (including those with hepatocellular carcinoma)	simeprevir + peginterferon alfa + ribavirin	12 weeks with 48 weeks of peg per guidelines
Recommended Treatment genotype 2		
Patients with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + ribavirin	12 weeks (patients with cirrhosis may benefit from an extension to 16 weeks of treatment)
Alternative Regimen genotype 2		
Patients (interferon eligible) with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + peginterferon alfa + ribavirin	12 weeks
Recommended Treatment genotype 3		
Patients with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + ribavirin	24 weeks
Alternative Regimen genotype 3		
Patients (interferon eligible) with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + peginterferon alfa + ribavirin	12 weeks
Recommended treatment genotype 4		
Patients (interferon eligible) with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + peginterferon alfa + ribavirin	12 weeks
Alternative Regimen genotype 4		
Patients with or without compensated cirrhosis (including those with hepatocellular carcinoma)	sofosbuvir + ribavirin	24 weeks
NOT RECOMMENDED (ALL GENOTYPES)		
Telaprevir, boceprevir, or any monotherapy with any agent		