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**Abbreviated Class Update:** Hepatitis C

**Month/Year of Review:** March 2014
**Current PDL Class:** Hepatitis C Agents

**Last Review:** September 2013
**Source Document:** OSU College of Pharmacy

- **Preferred Agents:** BOCEPREVIR (VICTRELIS®), TELAPREVIR (INCIVEK®), SOFOSBUVIR (SOLVALDI®), SIMEPREVIR (OLYSIO®), PEGINTERFERON ALPHA-2A (PEGASYS®), PEGINTERFERON ALPHA-2A SUBQ (PEGASYS®, PEGASYS PROCLICK®), PEGINTERFERON ALFA-2B, PEGINTERFERON ALFA-2B, RIBAVIRIN
- **Non-Preferred Agents**: INTERFERON ALFACON-1 (INGERGEN®), RIBAVIRIN DOSE-PACK (RIBAPAK®)

**Current PA:** Prior authorizations are currently in place or have been recommended for pegylated interferon and ribavirin (PR), for the oral protease inhibitors, and for sofosbuvir (Appendix 1) to ensure treatments are supported by the medical literature.

**Research Questions:**
- Is there any new evidence about comparative effectiveness of antiviral regimens, in long term clinical outcomes such as mortality and hepatitis C complications or in sustained virologic response (SVR) in adult patients being treated for chronic Hepatitis C virus (HCV)?
- Is there any new evidence about comparative harms of antiviral regimens in adult patients being treated for chronic HCV?
- Are there subpopulations of patients with HCV for which one antiviral regimen is more effective or associated with less harm?

**Conclusions:**
- In Genotype 1 treatment naïve patients and treatment experienced patients, there is insufficient to low quality evidence that simeprevir does not appear to significantly improve the SVR12 compared with triple therapy with boceprevir and telaprevir, and its effectiveness is diminished in patients with the Q80K genetic polymorphism in HCV genotype 1. [1] Simeprevir requires peginterferon and ribavirin (PR) and cannot be used to treat interferon-ineligible patients. There is an ongoing randomized trial comparing simeprevir to telaprevir is the first trial directly comparing 2 antiviral agents. Sofosbuvir therapy appears to have the highest SVR12 in this population (83%; 95% CI 79% to 87%).[1]
- There is insufficient evidence to evaluate the use of simeprevir or sofosbuvir in treatment-naïve genotype 1 patients who are interferon-ineligible.
- There is insufficient data to evaluate sofosbuvir plus ribavirin for genotype 1 treatment experienced patients or simeprevir plus PR.
- There is moderate quality evidence that in genotypes 2 and 3 CHC, sofosbuvir-based therapy improves SVR rates compared to dual therapy with pegylated interferon and ribavirin.
- There is low quality evidence, based on one unpublished open-label trial, that the combination of sofosbuvir plus simeprevir with or without ribavirin for 12 to 24 weeks results in high SVR12 rates (79-96%) in HCV genotype 1 null responders with METAVIR F0-F2 fibrosis.[2]

- There is insufficient evidence that the combination of sofosbuvir plus simeprevir with or without ribavirin for 12 to 24 weeks is efficacious in HCV genotype 2 treatment naïve and null responder patients with METAVIR F3-F4 fibrosis. Only preliminary data is available demonstrating SVR4 rates of 96-100%; SVR12 rates have not yet been released.[2]
- There is insufficient evidence evaluating the safety and efficacy of simeprevir in HCV patients with moderate or severe hepatic impairment. Clinical trials with simeprevir have been limited to patients with compensated disease who have CTP class A, total bilirubin level of 1.5 ULN or lower, and transaminase level of 10 x ULN or lower. It should be limited to patients with compensated liver disease.
- There is insufficient data evaluating sofosbuvir in patients with severe renal impairment (CrCl <30 ml/min) or those who require hemodialysis. There is no dosing data currently available for this patient population.

**Recommendations:**

- Recommend revising sofosbuvir prior authorization criteria for appropriate patient selection, including criteria to avoid in patients with significant renal impairment, those with decompensated liver disease, and those who would not be noncompliant for a variety of reasons (Appendix 1).
- Restrict sofosbuvir and simeprevir treatment to Fibrosis stage 3 and 4 patients at this time, consistent with recommendations from the community hepatology workgroup.
- Continue to evaluate new evidence as it comes out for further revisions.
- Develop and present a Readiness to Treat Assessment at next P&T meeting.

**Previous Conclusions and Recommendations:**

Class Update

- There is moderate strength evidence from a recent AHRQ report of a lower chance of achieving an SVR with dual therapy with pegylated interferon alfa-2b plus ribavirin compared to dual therapy with pegylated interferon alfa- 2a (pooled RR 0.87, 95% CI 0.80 to 0.95; I2=27.4%), with an absolute difference in SVR rates of 8 percentage points, while dual therapy with interferon alfa-2b is associated with a lower risk of serious adverse events than dual therapy with interferon alfa-2a (pooled RR 0.76, 95% CI 0.71 to 0.88; I2=0.0%) with no differences in withdrawals due to adverse events (pooled RR 1.1, 95% CI 0.73 to 1.7, I2=42%).
- There is high quality evidence that triple therapy with either boceprevir or telaprevir produces a higher likelihood of achieving SVR as compared to dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin.
- There is insufficient direct comparative evidence between boceprevir (BOC) and telaprevir (TVR) on long term clinical outcomes**.**

Sofosbuvir

- There is poor quality evidence, based on one open-label trial, that sofosbuvir in combination with ribavirin for 12 weeks is noninferior to pegylated interferon plus ribavirin for 24 weeks in genotype 2 and 3 treatment-naïve chronic Hepatitis C (CHC) in achieving SVR at week 12 (67% for both groups).
- There is moderate quality evidence that sofosbuvir in combination with ribavirin for 12 weeks is superior to placebo in genotype 2 and 3 CHC patients who are intolerant or ineligible for interferon based therapy in achieving SVR at week 12 (78% vs. 0%; p<0.001), as well as in patients who did not have a response to interferon therapy.
- There is evidence that extending the duration of treatment in genotype 3 patients to 24 weeks improves SVR rates compared to 12 weeks of treatment. Across all studies, genotype 2 patients achieved consistently higher SVR rates than genotype 3 patients.
- In genotype 1, there low quality evidence that the combination of sofosbuvir plus ribavirin plus peginterferon alfa results in higher rates of SVR at 12 weeks than historical control rates (90% vs. 60%). This is based on a single arm, open-label study.

- Based on limited data, sofosbuvir appears to have no serious adverse event concerns associated with its use and is well-tolerated for 12-16 weeks. The most common adverse events (>20%) of sofosbuvir in combination with ribavirin were fatigue and headache. The most common adverse events in combination with peginterferon alfa and ribavirin were fatigue, headache, nausea, insomnia, and anemia. Overall discontinuations due to adverse events in trials were low (0-2%).

Simeprevir

- There is evidence that simeprevir in combination with peginterferon alfa and ribavirin significantly improves SVR rates compared to placebo in patients with genotype 1 CHC, in both treatment- naïve patients (80% vs. 50%) and treatment experienced (79% vs. 36%, respectively). Most of the data remains unpublished and cannot be assessed for quality.
- There is low quality evidence, based on one phase IIb trial, that simeprevir in combination with peginterferon alfa and ribavirin is effective in achieving SVR in partial and null responders.
- Compared to placebo, there is low quality evidence that simeprevir does not significantly improve SVR rates in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline. Screening patients with HCV genotype 1 for the presence of this polymorphism is strongly recommended and alternative therapy should be considered for patients infected with the Q80K polymorphism.
- There is insufficient evidence evaluating simeprevir in patients who have previously failed therapy with a treatment regimen that includes simeprevir or other HCV protease inhibitors.
- There is insufficient evidence evaluating the use of simeprevir in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).The combination of simeprevir should not be used in patients with decompensated cirrhosis (moderate to severe hepatic impairment).
- There is low quality evidence of an increased risk of adverse reactions in patients of East Asian ancestry due to higher simeprevir exposure.

**Reason for Review:** New clinical practice guidelines for the treatment of chronic Hepatitis C were recently released. With the approval of the two new oral agents, these guidelines as well as any new evidence within the class will be reviewed for further decision-making.

**Background:**

Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma.[3] The goal of treatment for CHC is to prevent these long-term health complications. However, it remains difficult to design long term clinical trials that are large enough to provide direct evidence for these outcomes. The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels following completion of antiviral treatment. It is the standard marker of successful treatment in clinical trials and is associated with the long-term absence of viremia. There is some evidence of an association of achieving an SVR and reductions in mortality, liver failure, and cancer. [3] The two major predictors of SVR are viral genotype and the pretreatment viral load. Other factors associated with an increased likelihood of achieving an SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy. Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. The studies evaluating sofosbuvir use SVR at week 12 of follow-up (SVR12) as the primary endpoint, based on evidence that the majority of patients who have an SVR at week 12 maintain it until week 24.[4]

In the United States, genotype 1 infection is found in around three-quarters of patients and is associated with a lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20% of patients. [3] Current standard of care for Genotype 1 CHC is a protease inhibitor (boceprevir or telaprevir) plus pegylated interferon and ribavirin.[5] This is based on several RCTs showing improved rates of SVR (63-79%) with triple therapy compared to the previous standard of care of pegylated interferon and ribavirin dual therapy (55-60%). There is no direct comparative evidence on the effectiveness of the

currently available protease inhibitors. However, these agents come with several safety concerns and still depend on combination therapy with interferon and ribavirin which can result in serious adverse reactions. There are also important drug interactions seen with these protease inhibitors. For genotypes 2 and 3, the standard of care is still dual therapy with pegylated interferon and ribavirin for 24 weeks, which has shown SVR rates of 71-75% in genotype 2 and 61-66% in genotype 3.[6]

Simeprevir is a recently approved protease inhibitor used in combination with pegylated interferon and ribavirin for the treatment of adult patients with genotype 1 CHC. This includes patients with compensated liver disease, including patients with cirrhosis, who are treatment-naïve or who failed prior interferon therapy with or without ribavirin. There are trials underway evaluating its use in genotype 4 infection and HCV/HIV co-infection. Studies investigating the use of simeprevir as part of interferon-free regimens have also been intiated.[7] Simeprevir structurally binds to a target enzyme which is different than telaprevir and boceprevir (14-membered macrocycle). It is given orally once a day with any type of food for 12-48 weeks depending on whether the patient is treatment-naïve, a prior relapse, or a nonresponder.

Sofosbuvir is a nucleotide inhibitor of HSV NS5B RNA-dependent RNA polymerase with broad genotypic activity. Sofosbuvir was given breakthrough therapy designation as the first potential interferon-free CHC therapy from the FDA that allowed an expedited approval program.[4] The criteria for a breakthrough therapy designation from the FDA is that a) it is used for a serious condition, and b) preliminary clinical evidence demonstrates substantial improvement over available therapy on one more clinically significant endpoints. Unlike the other available protease inhibitors, there is no response guided therapy criteria for its use.

**Methods:**

A Medline literature search beginning September 2013 (since the most recent Hepatitis C Class Update) and ending February 2014 for new systematic reviews and randomized controlled trials (RCTs) that compared antiviral regimens and oral protease inhibitors, including boceprevir (BOC), telaprevir (TVR), simeprevir (SIM), and sofosbuvir (SOF) was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. The initial literature search resulted in 83 citations. After further review and exclusion of studies with drugs not yet FDA approved or already reviewed in preliminary SIM and SOF reviews, the search resulted in 7 RCTs[8–14], 2 systematic reviews[1,15], and 2 updated clinical practice guidelines.[16,17]

**Systematic Reviews:**

A draft technology report from the Institute for Clinical and Economic Review (ICER) was published in February 2014.[1] The assessment attempted to answer the following questions: 1) among patients with genotype 1, are treatment regimens incorporating the new DAAs equivalent or superior to the current standard of care, pegylated interferon plus ribavirin and one of the protease inhibitors; 2) among patients with genotypes 2 and 3, is the combination of sofosbuvir and ribavirin equivalent or superior to the current standard of care, pegylated interferon plus ribavirin; and 3) among interferon-ineligible or intolerant patients, is the combination of sofosbuvir plus ribavirin or sofosbuvir plus simeprevir equivalent or superior to no treatment. There were no studies found that directly compared therapies based on simeprevir to those based on sofosbuvir or to the two protease inhibitors boceprevir and telaprevir. A network meta-analysis was done to provide indirect evidence about the relative efficacy for the drug combinations available using these therapies.

The literature search identified 327 potentially relevant studies, resulting in 21 included publications describing simeprevir or sofosbuvir. Due to the paucity of literature, unpublished trials were included as well. All of the studies excluded patients with HIV, hepatitis B, or other significant illnesses. Results from the network meta-analyais for SVR12 among treatment naive patients infected with HCV genotype 1 are included in the following table:

| **Treatment** | **SVR12** | **95% CI** | **P versus PR** |
|---|---|---|---|
| PR | 47% | 41% to 52% | - |
| Boceprevir + PR | 73% | 68% to 77% | <0.001 |
| Telaprevir + PR | 74% | 69% to 79% | <0.001 |
| Simeprevir + PR | 76% | 70 to 81% | <0.001 |
| Sofosbuvir + PR | 83% | 79% to 87% | <0.001 |

PR: pegylated interferon + ribavirin

This suggests that simeprevir has similar SVR12 results compared to triple therapy with boceprevir or telaprevir and sofosbuvir therapy has the highest estimated SVR12. However, this is based on many assumptions as well from uncontrolled trials and therefore the evidence remains insufficient to make definitive conclusions regarding the comparative effectiveness of the agents. There were no studies for interferon-ineligible patients in treatment naïve patients.

For genotype 1 treatment experienced patients, again SVR 12 for simeprevir based therapy (67%; 95% CI 59-74%) was similar as that for triple therapy with boceprevir (64%; 95% CI 40-76%) and telaprevir (70%; 95% CI 61-77%). The combination of simeprevir plus sofosbuvir had the highest estimated SVR12 (90%; 95% CI 78-96%) but this is based on extrapolations from one uncontrolled trial and therefore the uncertainty of the results remains low. There were no studies in treatment-experienced patients who were interferon-ineligible. However, the combination of simeprevir and sofosbuvir evaluated four interferon-free regimens in treatment-experienced patients. The authors concluded that there is insufficient data to evaluate sofosbuvir plus ribavirin for genotype 1 treatment experienced patients and no data on sofosbuvir plus PR.

For genotype 2, the SVR24 for PR alone has shown to be 75-85%. Of the newer agents, only sofosbuvir has been approved for the treatment of genotypes 2 and 3. In genotype 2 treatment-naïve patients, there were a total of 8 studies (7 in interferon-eligible and 1 in interferon-ineligible). Sofosbuvir demonstrated an improvement in SVR over the previous standard of care, treatment time is decreased from 24 to 12 weeks, and interferon is no longer needed. It has also been studied in patients unwilling, unable, or intolerant of interferon. For treatment-experienced patients none of the trials had a control group without sofosbuvir. For genotype 3 treatment-naïve and treatment experienced patients, 24 weeks of sofosbuvir plus ribavirin appears to be superior to 12 or 16 weeks of the same therapy. The POSITRON data suggest that sofosbuvir plus ribavirin is effective for interferon-ineligible patients with genotype 3 and the VALENCE trial suggests that 24 weeks of therapy would be more effective than 12 weeks.

Overall, the authors noted that the addition of simeprevir to PR did not markedly increase the risk of adverse events. It was more difficult to assess the relative impact of sofosbuvir on adverse events because few of the trials randomized patients to a regimen without sofosbuvir. The most common adverse events in genotype 1 patients on sofosbuvir and PR included fatigue, headache, and flu-like illness and fewer patients stopped therapy due to adverse events than those in

the PR group (2% vs. 11%). In genotype 2 and 3 patients, the elimination of interferon from the treatment regimen markedly decreased the risk for most adverse events. There were also significantly fewer grade 3 or 4 adverse events, and a reduction in discontinuation of therapy due to adverse events.

Pegylated Interferon:

A systematic search including randomized, prospective studies compared rapid virological response (RVR) and early virological response (EVR) rates of peginterferon alfa-2a vs. peginterferon alfa-2b.[15] A total of 8 RCTs were included in the meta-analysis. The early virological response meta-analysis included 7 trials and 4359 patients and showed an overall significant increase in the percentage of patients treated with peginterferon alfa-2a that achieved EVR when compared with the peginterferon alfa-2b group (53.3% vs. 43.8%; p=0.0028). The meta-analysis of RVR included 5 trials and 3833 patients with an estimated effect in favor of peginterferon alfa-2a of 25% vs. 16.8% for peginterferon alfa-2b (p=0.0056).

**Clinical Guidelines:**

On January 29, 2014, the American Association for the Study of Liver Diseases (AASLD) / Infectious Diseases Society of America (IDSA) / International Antiviral Society (IAS) jointly created guidelines for the treatment of chronic hepatitis C.[17] The Guidance was developed by a panel of HCV experts in the fields of hepatology and infectious diseases, but did lack non-specialist members. Recommendations were graded in terms of the level of the evidence and strength of the recommendation, using a scale adapted from the American College of Cardiology and the American Heart Association Practice Guidelines. The main recommendations are as followed:

**Treatment naïve or those who experienced relapse after prior treatment with peginterferon and ribavirin:**

*Genotype 1, interferon eligible*

1. Initial therapy with sofosbuvir plus PR for 12 weeks (Class 1, Level A recommendation).
    a. This is based on one poor quality, open-label, single-arm phase 3 NEUTRINO trial evaluating sofosbuvir in combination with pegylated interferon and ribavirin in 291 treatment-naïve patients with HCV genotype 1 infection. The SVR 12 was 89% and was lower in patients with cirrhosis.
2. Alternative regimens include daily simeprevir + PR for 12 weeks (for only those with HCV genotype 1b or HCV genotype 1a without the Q80K polymorphism). (Class IIA, Level A recommendation).
    a. The alternative regimen is based on two unpublished, randomized, placebo controlled phase 3 trials evaluating the efficacy and safety of simeprevir
3. Treatment with telaprevir or boceprevir is NOT recommended (Class IIB, Level A recommendation).
4. Monotherapy with pegylated interferon, ribavirin, or a direct acting antiviral are not recommended (Class III, Level A recommendation).

*Genotype 1, interferon ineligible*

1. Sofosbuvir plus simeprevir, with or without ribavirin for 12 weeks is recommended (Class I, Level B recommendation)
    a. This is based on the unpublished ongoing phase 2 COSMOS trial. This regimen should only be considered in patients who require immediate treatment.
2. Alternative regimen of sofosbuvir plus ribavirin for 24 weeks (Class IIb, Level B recommendation).
    a. This is based on one, poor quality, phase 2, open-label clinical trial in 60 treatment-naïve patients with unfavorable characteristics (African American race and advanced fibrosis).

*Genotype 2*

1. Sofosbuvir plus ribavirin for 12 weeks (Class I, Level A recommendation). There are no recommended alternative regimens.
    a. This is based on 2 fair quality and one unpublished phase 3 trials. Across all 3 trials, 94% of patients achieved SVR with sofosbuvir plus ribavirin.

*Genotype 3*

1. Sofosbuvir plus ribavirin for 24 weeks (Class I, Level B recommendation)
    a. One unpublished trial (VALENCE) demonstrated that higher response rates can be achieved with a 24-week duration of sofosbuvir than those reported for the 12 or 16 week durations studied in other trials (84% vs. 61%, respectively).
2. Alternative regimen is sofosbuvir plus ribavirin plus peginterferon alfa for 12 weeks.
    a. Two unpublished trials (PROTON and ELECTRON) have evaluated the combination of sofosbuvir + PR in patients with genotype 3 HCV and demonstrated a 97% SVR rate in treatment-naïve patients. This regimen has a higher risk of adverse effects and may require increased monitoring.

*Genotype 4, interferon eligible*

1. Sofosbuvir + PR is recommended for 12 weeks (Class IIa, Level B recommendation). Few data is available for genotype 4 and only patients who immediate treatment is required should be treated.
    *a.* This is based on one poor quality, open-label, single arm study (NEUTRINO) evaluating 12 weeks of sofosbuvir. Of the 28 patients with genotype 4, 27 (96%) achieved SVR12.
2. Alternative regimen of simeprevir for 12 weeks plus ribavirin and peginterferon for 24-48 weeks is recommended (Class IIB, level B recommendation).
    *a.* This is based on one ongoing phase 3 trial in patient with genotype 4.

*Genotype 4, interferon ineligible*

1. Sofosbuvir plus ribavirin for 24 weeks is recommended (Class IIB, Level B recommendation).
    a. This is based on a small, unpublished study of Egyptian patients in the U.S. treated with sofosbuvir plus ribavirin. SVR 12 was achieved in 11 of 14 (79%) treatment-naïve patients treated for 12 weeks. SVR24 was achieved in 100% of the 14 treatment-naïve patients treated for 24 weeks.

**Retreatment of persons in whom prior therapy has failed (non-responders, including null responders and partial responders):**

*Genotype 1 nonresponders*

1. Initial therapy with sofosbuvir plus simeprevir, with or without ribavirin for 12 weeks (Class IIA, Level B recommendation).
    a. This is based on the unpublished, phase 2a, randomized trial (COSMOS) evaluating the combination of sofosbuvir plus simeprevir with or without weight based ribavirin for 12 or 24 weeks. Of the 80 null responders with a Metavir fibrosis stage of 2 or less, 79% to 96% achieved SVR. Among those null responders with a Metavir fibrosis stage of 3 or 4 (n=47), SVR4 was observed in 93% of the 15 patients in the ribavirin containing arm and 100% of the 7 participants in the ribavirin-free arm. SVR 12 data is not yet available for this cohort of patients. This should not be used in those who have had previous treatment with either telaprevir or boceprevir.
2. Alternative regimens include daily sofosbuvir for 12 weeks and PR for 12-24 weeks (Class IIB, Level C recommendation).
    a. The alternative regimen is based on very limited data, including a poor quality, single arm, open-label trial (NEUTRINO) that evaluated 12 weeks of sofosbuvir in treatment-naïve subjects. Although treatment-experienced subjects were not included in this study, FDA estimates that the response rate in such patients would approximate the observed response rate in those in the NEUTRINO trial with baseline factors traditionally associated with a lower response to interferon-based treatment.
3. Alternative regimen includes simeprevir for 12 weeks plus PR for 48 weeks; all patients with cirrhosis who are receiving simeprevir should have well compensated liver disease (Class IIa, Level A recommendation).

a. The ASPIRE trial is a phase 2b recently published trial evaluating simeprevir + PR in patients who had previously failed to respond to dual therapy.[14] SVR24 after 48 weeks of triple therapy in the simeprevir 150 mg/day arm was 65% in patients with a previous partial response (n=23) and 53% in patients with a prior null response (n=17).

4. Treatment with telaprevir or boceprevir is NOT recommended (Class IIB, Level A recommendation).

*Genotype 2, nonresponders*

1. Sofosbuvir + ribavirin for 12 weeks; patients with cirrhosis may benefit by extension of treatment to 16 weeks (Class 1, Level A recommendation).
2. Sofosbuvir + PR for 12 weeks (Class IIa, Level B recommendation).
    a. The LONESTAR-2 trial is an unpublished, open-label, single site, single-arm phase 2 trial evaluating triple therapy with sofosbuvir in treatment-experienced patients with HCV genotype 2 or 3.

*Genotype 3, nonresponders*

1. Sofosbuvir plus ribavirin for 24 weeks (Class IIa, Level A recommendation)
2. Alternative regimen includes retreatment with sofosbuvir + PR for 12 weeks.

**EASL Clinical Practice Guidelines:**

In December 2013, the European Association for the Study of the Liver (EASL) updated its HCV treatment guidelines.[16] These guidelines were developed by a panel of experts and peer-reviewed by external expert reviewers. They were established using evidence and when not available, experts' experiences and opinion. The GRADE system was used to evaluate the strength of recommendations. These guidelines did not include the new agents, sofosbuvir and simeprevir, and are therefore outdated. Relevant guidelines regarding initiation of therapy are included as follows:

- All treatment-naïve patients with compensated disease due to HCV should be considered for therapy (recommendation A1).
- Treatment should not be deferred for patients with significant fibrosis, METAVIR score F3 to F2 (recommendation A1).
- In patients with less severe disease, the indication for and timing of therapy can be individualized (recommendation B1).

**Simeprevir and Sofosbuvir Combination Therapy:**

There is one small unpublished phase IIa study (COSMOS) evaluating the combination of simeprevir and sofosbuvir in the treatment of previous null responders and treatment naïve patients.[2] Currently, only the abstract is available. The study is an open-label, randomized, phase II study in genotype 1 patients (n=167) with METAVIR scores F0-F2 who were prior null responders to PR (Cohort 1) or treatment-naïve patients and prior null responders with F3-F4 (Cohort 2). Patients in both cohorts were also randomized to simeprevir + sofosbuvir (with or without ribavirin for 12 weeks of simeprevir + sofosbuvir (with or without ribavirin) for 24 weeks. SVR 12 rates in the F0-F2 groups ranged from 79.2% to 96.3%. The lowest SVR 12 was in the most intense (24 weeks of the combination with ribavirin) treatment group and appears to be due to participants lost to follow-up, but the details of the data are not clear at this point. The highest SVR12 rate was in the simeprevir + sofosbuvir + ribavirin for 12 weeks group and SVR 12 was only 88.9% in those with the Q80K polymorphism. The results in the Cohort 2 patients with METAVIR F3-F4 fibrosis scores have not been released yet, although the preliminary SVR4 rates appear high. This preliminary data suggests that there may be no benefit from adding ribavirin to simeprevir and sofosbuvir and that 12 weeks of treatment may results in similar benefits compared to 24 week treatment. The most common adverse events were fatigue, headache, and nausea and anemia occurred mostly in the ribavirin-containing treatment groups.

**Randomized Controlled Trials:**

Seven potentially relevant RCTs were evaluated from the literature search. After further review, 2 RCTs[8,9] included drugs not yet FDA approved and were therefore excluded, and one was a phase I study of boceprevir in HCV 2 and 3 genotype isolates assays and was also excluded.[10] The remaining 4 RCTs are briefly described in the table below. Abstracts of these trials are found in Appendix 2:

| Study | Comparison | Population | Primary Outcome | Results |
|---|---|---|---|---|
| Zeuzem et al.[14]<br>RCT, Phase IIb, DB, PC | Simeprevir 12-48 weeks + PR vs. PR x 48 weeks | HCV genotype 1, non-responders to dual therapy with peginterferon and ribavirin | SVR at week 24 (SVR24) | <u>SVR24</u><br>SIM: 60.6%-80%<br>Pla: 22.7%<br>P<0.001<br><br><u>Null responders:</u><br>SIM: 37.5-58.8%<br>Pla: 18.8%<br><br><u>Partial responders:</u><br>SIM: 47.8%-86.4%<br>Pla: 8.7%<br><br><u>Relapsers</u><br>SIM: 76.9-88.9%<br>Pla: 37% |
| Liu et al.[11]<br>Open-label, RCT | Pegylated interferon-alfa2a plus ribavirin vs. pegylated interferon alfa2a monotherapy x 48 weeks<br>(n=205) | Treatment-naïve patients with HCV genotype 1 receiving hemodialysis | SVR24 | <u>SVR24</u><br>Peg + Rib: 66/103 (64%)<br>Peg alone: 34/102 (33%)<br>RR 1.92; 95% CI 1.41-2.62<br>P<0.001 |
| Rodriguez-Torres et al.[12], RCT, DB, dose-ranging | Sofosbuvir (100, 200, or 400 mg) vs. placebo + PR x 28 days, followed by 44 weeks of PR alone | Treatment-naïve, HCV genotype 1, non-cirrhotic | SVR24 | <u>SVR24</u><br>Sof 100: 56%<br>Sof 200: 83%<br>Sof 400: 80%<br>PR: 43%<br>Peg alone: 34/102 (33%)<br>RR 1.92; 95% CI 1.41-2.62<br>P<0.001 |
| Benhamou et al.[13]<br>Phase 2a, partially blinded, RCT | Telaprevir 750 mg every 8 hours vs. telaprevir + PR vs. PR + placebo x 15 days<br>(n=24) | Treatment-naïve, HCV genotype 4 | The effect of telaprevir on early viral kinetics | <u>SVR at the end of treatment</u><br>Telaprevir: 62.5%<br>Telaprevir + PR: 50%<br>PR: 62.5% |

Ongoing Trials:

A randomized trial comparing simeprevir to telaprevir in treatment-experienced patients is underway. This will be the first study to compare the new DAAs to the current standard of care for treating HCV genotype 1.[1]

References:


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Appendix 1: Prior authorization Criteria

# Sofosbuvir (Sovaldi®)

**Goal(s) :**

- Approve cost effective treatments of chronic hepatitis C which are supported by the medical literature and where there is medical evidence of effectiveness and safety

Length of Authorization

- Initial trial of 12 weeks
- Continuation of therapy up to 24-48 weeks of total therapy based on therapy regimen, genotype, and patient population

**Requies PA:**

- Sofosbuvir

| **Approval Criteria** | | |
|---|---|---|
| 1. Is the request for treatment of Chronic Hepatitis C?<br>Document appropriate ICD9 code: | **Yes:** Go to #2 | **No:** Pass to RPh, Deny For Appropriateness |
| 2. Is the request for continuation of therapy? | **Yes:** Go to "Continuation of Therapy" | **No:** Go to #3 |
| 3. Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C? | **Yes:** Go to #4 | **No:** Pass to RPh, Deny For Appropriateness |
| 4. If the patient has been treated with peginterferon and ribavirin before, do they have documented noncompliance to their previous treatment? | **Yes:** Pass to RPh, Deny For Appropriateness | **No:** Go to #5 |
| 5. Does the patient have a biopsy or other non-invasive technology (Fibroscan), including serum tests (Fibrosure, Fibrotest) to indicate severe fibrosis (stage 3 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins).<br><br>Note: Occasional patients with HCV and hepatocellular carcinoma who do not have advanced fibrosis (Stage 3-4) should be included for treatment. Discuss with physician to confirm these particular cases. | **Yes:** Go to #6 | **No:** Pass to RPh, Deny For Appropriateness |
| 6. Does the patient have a HIV coinfection? | **Yes:** Go to #7 | **No:** Go to #8 |
| 7. Is the patient under the supervision of an HIV specialist? | **Yes:** Go to #8 | **No:** Pass to RPh; Deny (medical appropriateness) |

| | | |
|---|---|---|
| 8. If applicable, has the patient been abstinent from IV drug use or alcohol abuse for ≥ 6 months? | **Yes**: Go to #9 | **No:** Pass to RPh, Deny for appropriateness |
| 9. Does the patient have significant renal impairment (CrCl < 30 ml/min) or end stage renal disease (ESRD)? | **Yes:** Pass to RPh; Deny for appropriateness | **No:** Go `to #10 |
| 10. What Hepatitis C genotype is the patient?<br>Record Genotype: | Record Genotype and go to #11 | |
| 11. Does the patient have genotype 1 or 4 chronic hepatitis C? | **Yes:** Go to # 12 | **No:** Go to #15 |
| 12. Is the medication being used as triple therapy with both ribavirin and peginterferon alfa? | **Yes:** Approve for 12 weeks total therapy | **No:** Go to #13 |
| 13. Is the medication being used with ribavirin or simeprevir? | **Yes:** Go to #14 | **No:** Pass To Rph; Deny for Appropriateness |
| 14. Is the patient interferon ineligible defined by having one of the following conditions:<br>• Previous adverse reaction or hypersensitivity to interferon<br>• Decompensated liver disease<br>• Severe or uncontrolled psychiatric disorder in consult with a psychiatrist<br>• Autoimmune hepatitis or other autoimmune disorders<br>• Unstable cardiac disease<br><br>Note: Patient's or prescribers not wanting to go through treatment with interferon does not meet the criteria for being "interferon ineligible" | **Yes:** Approve initial trial of 12 weeks for total therapy of 12 weeks for sofosbuvir + simeprevir combination **OR** a total of 24 weeks for sofosbuvir + ribavirin therapy | **No:** Pass To Rph; Deny for Appropriateness |
| 15. Does the patient have genotype 2 chronic hepatitis C? | **Yes:** Go to #16 | **No:** Go to #17 |
| 16. Is the medication being used with ribavirin? | **Yes:** Approve for 12 weeks total therapy | **No:** Pass To Rph; Deny for Appropriateness |
| 17. Does the patient have genotype 3 chronic hepatitis C? | **Yes:** Go to #18 | **No:** Pass To Rph; Deny for Appropriateness |
| 18. Is the medication being used with both ribavirin and peginterferon alfa? | **Yes:** Approve for 12 weeks total therapy | **No:** Go to #19 |
| 19. Is the medication being used with only ribavirin and the patient is interferon ineligible as defined by the conditions listed above in #15? | **Yes:** Approve for 12 weeks initial fill for a total 24 weeks of therapy | **No:** Pass To Rph; Deny for Appropriateness |

*P&T Board Action: 1/30/13 (MH)*
*Revision(s): 3/27/13*
*Initiated:*

## Continuation of Therapy- Sofosbuvir

| | | |
|---|---|---|
| Has the patient been adherent to and tolerated initial therapy? | **Yes**: Approve for additional 12 weeks in genotype 3 patients and genotype 1 patients who are interferon ineligible (refer to dosage and administration table below). | **No:** DENY<br>(Medical Appropriateness) |

## Hepatitis C Oral Protease Inhibitors/Triple Therapy

**Goal(s) :**

- Approve treatments of chronic hepatitis C which are supported by the medical literature

Length of Authorization

- Initial trial of 8-12weeks (depending on regimen)
- Continuation of therapy up to 48 weeks of total therapy

**Requires PA:**

- Telaprevir
- Boceprevir
- Simeprevir

| **Approval Criteria** | | |
|---|---|---|
| 1. Is the request for treatment of Chronic Hepatitis C?<br>Document appropriate ICD9 code: | **Yes:** Go to #2 | **No:** Pass to RPh, Deny For Appropriateness |
| 2. Does the patient have documented HCV genotype 1?<br>Record Genotype: | **Yes:** Go to #3 | **No:** Pass to RPh, Deny For Appropriateness |
| 3. Is the prescription for simeprevir? | **Yes: Go to #4** | **No: Go to #6** |
| 4. Has the patient been screened for the presence of virus with the NS3 Q80K polymorphism at baseline? | **Yes: Go to #5** | **No:** Pass to RPh, Deny For Appropriateness. Recommend that the screening take place. |
| 5. Does the patient have the genotype 1 Q80K polymorphism virus? | **Yes:** Pass to RPh, Deny for Appropriateness | **No:** Go To #6 |

| | | |
|---|---|---|
| 6. Is the patient also being prescribed peginterferon alfa-2a or -2b and ribavirin and has been granted prior authorization or meets criteria for pegylated interferon-alfa and ribavirin? | **Yes:** Go to #7 | **No:** Pass to RPh, Deny For Appropriateness |
| 7. Is the request for continuation of therapy? (Patient has been on triple therapy with an oral antiviral agent in preceding 6 weeks) | **Yes**: Go to "Continuation of Therapy | **No**: Go to #8 |
| 8. Does the patient have a Child-Pugh score < 7 (compensated liver disease)? | **Yes:** Go to #9 | **No:** Pass to RPh, Deny For Appropriateness |
| 9. Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C? | **Yes:** Go to #10 | **No:** Pass to RPh, Deny For Appropriateness |
| 10. If the patient has been treated with peginterferon and ribavirin before, do they have documented compliance/adherence to their previous treatment? | **Yes:** Go to #11 | **No:** Pass to RPh, Deny For Appropriateness |
| 11. Does the patient have a biopsy to indicate moderate to severe fibrosis (Metavir score of 2 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins)?. | **Yes:** Go to #12 | **No:** Pass to RPh, Deny For Appropriateness |
| 12. Does the patient have a HIV coinfection? | **Yes:** Go to #13 | **No:** Go to #14 |
| 13. Is the patient under the supervision of an HIV specialist? | **Yes:** Go to #14 | **No:** Pass to RPh; Deny (medical appropriateness) |
| 14. Has the patient previously been treated with boceprevir, telaprevir, or simeprevir? | **Yes**: Pass to RPh, Deny for appropriateness | **No:** Go to #15 |
| 15. Is the request for telaprevir 750mg (two tabs) TID for 12 weeks? | **Yes:** Approve for 8 weeks to allow for 4 week viral load check to continue for a maximum of 12 weeks | **No:** Go to #16 (If dose is different pass to RPh for appropriateness) |
| 16. Is the request for boceprevir 800mg (four tabs) TID and the patient has completed 4 weeks of lead-in treatment with ribavirin and peginterferon? | **Yes:** Approve for 12 weeks to allow for 8 week viral load check to continue for a maximum of 24, 32, or 40 weeks based on response | **No:** Go to #17 (If dose is different pass to RPh for appropriateness) |
| 17. Is the request for simeprevir 150 mg once daily for 12 weeks? | **Yes: Approve for 8 weeks to allow for 4 weeks viral load check to continue for a maximum of 12 weeks** | **No: Pass to RPh; Deny for appropriateness** |

## Continuation of Therapy- Telaprevir

| | | |
|---|---|---|
| **1.** Is the patient treatment-naïve or a prior relapse patient and has undetectable HCV RNA or measured at 4 and 12 weeks? | **Yes:** Approve as follows:<br>• Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks). | **No:** DENY<br>(Medical Appropriateness)<br><br>Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24. |
| **2.** Is the patient treatment-naïve or a prior relapse patient and has detectable (1000 IU/mL or less) at Weeks 4 and/or 12 | **Yes:** Approve as follows:<br>• Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks). | **No:** DENY<br>(Medical Appropriateness)<br><br>Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24. |
| **3.** Is the patient a prior partial or null responder? | **Yes:** Approve as follows:<br>• Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks). | **No:** DENY<br>(Medical Appropriateness) |
| **4**. Is the patient treatment-naïve with documented cirrhosis that has undetectable HCV-RNA at weeks 4 and 12? | **Yes:** Approve as follows:<br>• Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks). | **No:** DENY<br>(Medical Appropriateness)<br><br>Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24. |
| ***TREATMENT FUTILITY RULES**<br>Week 4 or Week 12: HCV-RNA greater than 1000 IU/mL: Discontinue INCIVEK and peginterferon alfa and ribavirin (INCIVEK treatment complete at 12 weeks)<br>Week 24: Detectable Discontinue peginterferon and ribavirin.<br>If peginterferon alfa or ribavirin is discontinued for any reason, INCIVEK must also be discontinued | | |

| Continuation of Therapy- Boceprevir | | |
|---|---|---|
| **1.** Is the patient treatment-naïve and have undetectable HCV RNA at treatment weeks 8 and 24? | **Yes:** Approve as follows:<br>• Approve additional 14 weeks of boceprevir for total treatment duration of 28 weeks (4 week lead-in, 24 weeks triple therapy) | **No:** DENY<br>(Medical Appropriateness) |
| **2.** Is the patient treatment-naïve and have detectable HCV RNA at treatment week 8 and undetectable at week 24? | **Yes:** Approve as follows:<br>• Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy) | **No:** DENY<br>(Medical Appropriateness) |
| **3.** Is the patient a previous partial responder or relapser and has undetectable HCV RNA at treatment weeks 8 and 24? | **Yes:** Approve as follows:<br>• Approve additional 22 weeks of boceprevir for total treatment duration of 36 weeks (4 week lead-in, 32 weeks triple therapy) | **No:** DENY<br>(Medical Appropriateness) |
| **4.** Is the patient a previous partial responder or relapser and has detectable HCV RNA at treatment week 8 and undetectable at week 24? | **Yes:** Approve as follows:<br>• Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy) | **No:** DENY<br>(Medical Appropriateness) |
| **5**. Does the patient have documented cirrhosis or is documented as a null responder and does not meet the futility rules at treatment weeks 8, 12, and 24? | **Yes:** Approve as follows:<br>• Continue triple therapy with boceprevir for a total treatment duration of 48 weeks (4 week lead-in, 44 weeks triple therapy). | **No:** DENY<br>(Medical Appropriateness) |

***TREATMENT FUTILITY RULES**
If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen.
If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.

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**Continuation of Therapy- Simeprevir:** Simeprevir in combination with peginterferon alfa and ribavirin should only be given for 12 weeks. No more simeprevir should be approved. The following are the recommended duration of treatments for dual therapy with peginterferon alfa and ribavirin after the initial 12 weeks of triple therapy

| | | |
|---|---|---|
| **1.** Is the patient treatment-naïve or a prior relapse and has undetectable HCV RNA (< 25 IU/ml) at week 4? | **Yes:** Approve as follows:<br>• Approve additional 4 weeks of simeprevir for total treatment duration of 12 weeks of triple therapy, followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks). | **No:** DENY<br>(Medical Appropriateness)<br><br>It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients. |
| **2.** Is the patient a prior non-responder (including partial and null responders) and has an undetectable HCV RNA (<25 IU/ml) at week 4? | **Yes:** Approve as follows:<br>• Approve additional 4 weeks of simeprevir for total treatment duration of 12 weeks of triple therapy, followed by continued dual therapy with peginterferon and ribavarin for 36 weeks (total treatment duration of 48 weeks). | **No:** DENY<br>(Medical Appropriateness)<br><br>It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients |

***TREATMENT FUTILITY RULES**
If the patient has HCV-RNA results greater than or equal to 25 IU/mL at TW12, then discontinue three-medicine regimen.
If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue two-medicine regimen.

*P&T Board Action: 1-26-2012*

# Interferons and Ribavirins

**Goal(s):**

**Cover drugs only for those clients where there is medical evidence of effectiveness and safety**

**Length of Authorization: 16 weeks plus 12-36 additional weeks or 12 months**

**Requires pa: All drugs in HIC3 = W5G**

**Preferred Alternatives:** See PDL list at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

| Approval Criteria | | |
|---|---|---|
| **1**. Is peginterferon requested preferred? | **Yes:** Go to #4 | **No:** Go to #2. |
| **2.** Will the prescriber consider a change to a preferred product?<br>Message:<br>- Preferred products are evidence-based reviewed for comparative effectiveness & safety Oregon Pharmacy and Therapeutics (P&T) Committee | **Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml. | **No:** Go to #3. |
| **3.** If the request is for interferon alfacon-1, does the patient have a documented trial of a pegylated interferon? | **Yes:** Go to #4. | **No:** Deny; Pass to RPH (Medical Appropriateness) |
| **4.** Is the request for treatment of Chronic Hepatitis C?<br>Document appropriate ICD9 code:<br>(571.40; 571.41; 571.49) | **Yes:** Go to #5. | **No:** Go to #11 |
| **5.** Is the request for continuation of therapy? (Patient has been on HCV treatment in the preceding 12 weeks according to the Rx profile) | **Yes:** Go to "Continuation of Therapy" | . **No:** Go to #6 |
| **6**. Does the patient have a history of treatment with previous pegylated interferon-ribavirin combination treatment?<br><br>Verify by reviewing member's Rx profile for PEG-Intron or Pegasys, PLUS ribavirin history. Does not include prior treatment with interferon | **Yes:** Forward to DMAP Medical Director | **No:** Go to #7 |

| | | |
|---|---|---|
| monotherapy or non-pegylated interferon. | | |
| **7**. Does the patient have any of the following contraindications to the use of interferon-ribavirin therapy?<br>• severe or uncontrolled psychiatric disorder<br>• decompensated cirrhosis or hepatic encephalopathy<br>• hemoglobinopathy<br>• untreated hyperthyroidism<br>• severe renal impairment or transplant<br>• autoimmune disease<br>• pregnancy<br>• unstable CVD | **Yes:** Deny; Pass to RPH (Medical Appropriateness) | **No:** Go to #8 |
| **8**. If applicable, has the patient been abstinent from IV drug use or alcohol abuse for ≥ 6 months? | **Yes:** Go to #9 | **No:** Deny; Pass to RPH (Medical Appropriateness) |
| **9**. Does the patient have a detectable HCV RNA (viral load) > 50IU/mL? Record HCV RNA and date: | **Yes:** Go to #10 | **No:** Deny; Pass to RPH (Medical Appropriateness) |
| **10**. Does the patient have a documented HCV Genotype?<br>Record Genotype: | **Yes:** Approve for 16 weeks with the following response: Your request for has been approved for an initial 16 weeks. Subsequent approval is dependent on documentation of response via a repeat viral load demonstrating undetectable or 2-log reduction in HCV viral load. Please order a repeat viral load after 12 weeks submit lab results and relevant medical records with a new PA request for continuation therapy.<br>Note: For ribavirin approve the generic only | **No:** Deny; Pass to RPH (Medical Appropriateness) |
| **11**. Is the request for Pegasys and the treatment of confirmed, compensated Chronic Hepatitis B? | **Yes:** Go to #11 | **No:** Deny; Pass to RPH (Medical Appropriateness) |
| **12**. Is the patient currently on LAMIVUDINE (EPIVIR HBV), ADEFOVIR (HEPSERA), ENTECAVIR (BARACLUDE), TELBIVUDINE (TYZEKA) and the request is for combination Pegasys-oral agent therapy? | **Yes:** Deny; Pass to RPH (Medical Appropriateness) | **No:** Go to #12 |
| **13**. Has the member received previous treatment with pegylated interferon? | **Yes:** Deny; Pass to RPH (Medical Appropriateness)<br>Recommend:<br>LAMIVUDINE (EPIVIR HBV)<br>ADEFOVIR (HEPSERA) | **No:** Approve<br>Pegasys #4 x 1ml vials or #4 x 0.5 ml syringes per month for 12 months (maximum per lifetime). |

## Continuation of Therapy- HCV

**1.** Does the client have undetectable HCV RNA or at least a 2-log reduction (+/- one standard deviation) in HCV RNA measured at 12 weeks?

**Yes:** Approve as follows:

Approval for beyond quantity and duration limits requires approval from the medical director.

| Genotype | Approve for | Apply |
|---|---|---|
| 1 or 4 | **An additional 36 weeks** or for up to a total of 48 weeks of therapy (whichever is the lesser of the two). | Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose =1200 mg). |
| 2 or 3 | **An additional 12 weeks** or for up to a total of 24 weeks of therapy (whichever is the lesser of the two). | Ribavirin quantity limit of 200 mg tab QS# 120 / 25 days (for max daily dose = 800 mg). |
| For all genotypes and HIV co-infection | **An additional 36 weeks** or for up to a total of 48 weeks of therapy (whichever is the lesser of the two) | Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose = 1200 mg). |

**No:** DENY
(Medical Appropriateness)

Treatment with pegylated interferon-ribarvirin does not meet medical necessity criteria because there is poor chance of achieving an SVR.

**Clinical Notes:**

- Serum transaminases: Up to 40 percent of clients with chronic hepatitis C have normal serum alanine aminotransferase (ALT) levels, even when tested on multiple occasions.
- RNA: Most clients with chronic hepatitis C have levels of HCV RNA (viral load) between 100,000 ($10^5$) and 10,000,000 ($10^7$) copies per ml. Expressed as IU, these averages are 50,000 to 5 million IU. Rates of response to a course of peginterferon-ribavirin are higher in clients with low levels of HCV RNA. There are several definitions of a “low level” of HCV RNA, but the usual definition is below 800,000 IU (~ 2 million copies) per ml.(5)
- Liver biopsy: Not necessary for diagnosis but helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage and for ruling out other causes of liver disease, such as alcoholic liver injury, nonalcoholic fatty liver disease, or iron overload.
-

| Stage is indicative of fibrosis: | | | Grade is indicative of necrosis: | |
|---|---|---|---|---|
| Stage 0 | No fibrosis | | | |
| Stage 1 | Enlargement of the portal areas by fibrosis | | Stage 1 | None |

| | | | | |
|---|---|---|---|---|
| Stage 2 | Fibrosis extending out from the portal areas with rare bridges between portal areas | | Stage 2 | Mild |
| Stage 3 | Fibrosis that link up portal and central areas of the liver | | Stage 3 | Moderate |
| Stage 4 | Cirrhosis | | Stage 4 | Marked |

**The following are considered investigational and/or do not meet medical necessity criteria:**

- ✓ Treatment of HBV or HCV in clinically decompensated cirrhosis
- ✓ Treatment of HCV or HBV in liver transplant recipients
- ✓ Treatment of HCV or HBV > 48 weeks
- ✓ Treatment of advanced renal cell carcinoma
- ✓ Treatment of thrombocytopenia
- ✓ Treatment of human papilloma virus
- ✓ Treatment of multiple myeloma

**Appendix 2: Abstracts of potentially relevant RCTs**

1. Zeuzem et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology. 2014 Feb;146(2):430-441.e6.

**Background & Aims**: Simeprevir (TMC435) is an oral NS3/4 protease inhibitor in phase III trials for chronic hepatitis C virus (HCV) infection. We performed a phase IIb, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of the combination of simeprevir, peginterferon-α2a (PegIFN), and ribavirin (RBV) in patients with HCV genotype-1 infection previously treated with PegIFN and RBV.

**Methods**: We analyzed data from patients who did not respond (null response), had a partial response, or relapsed after treatment with PegIFN and RBV, randomly assigned to receive simeprevir (100 or 150 mg, once daily) for 12, 24, or 48 weeks plus PegIFN and RBV for 48 weeks (n = 396), or placebo plus PegIFN and RBV for 48 weeks (n = 66). All patients were followed for 24 weeks after planned end of treatment; the primary end point was the proportion of patients with sustained virologic response (SVR; undetectable HCV RNA) at that time point.

**Results**: Overall, rates of SVR at 24 weeks were significantly higher in the groups given simeprevir than those given placebo (61%−80% vs 23%; $P < .001$), regardless of prior response to PegIFN and RBV (simeprevir vs placebo: prior null response, 38%−59% vs 19%; prior partial response, 48%−86% vs 9%; prior relapse, 77%−89% vs 37%). All groups had comparable numbers of adverse events; these led to discontinuation of simeprevir or placebo and/or PegIFN and RBV in 8.8% of patients given simeprevir and 4.5% of those given placebo.

**Conclusions**: In treatment-experienced patients, 12, 24, or 48 weeks simeprevir (100 mg or 150 mg once daily) in combination with 48 weeks PegIFN and RBV significantly increased rates of SVR at 24 weeks compared with patients given placebo, PegIFN, and RBV and was generally well tolerated

2. Liu CH et al. Pegylated interferon-α2a with or without low-dose ribavirin for treatment-naive patients with hepatitis C virus genotype 1 receiving hemodialysis: a randomized trial. Ann Intern Med. 2013 Dec 3;159(11):729-38

**BACKGROUND:** Data are limited on the efficacy and safety of pegylated interferon plus ribavirin for patients with hepatitis C virus genotype 1 (HCV-1) receiving hemodialysis.

**OBJECTIVE:** To compare the efficacy and safety of combination therapy with pegylated interferon plus low-dose ribavirin and pegylated interferon monotherapy for treatment-naive patients with HCV-1 receiving hemodialysis.

**DESIGN:** Open-label, randomized, controlled trial. (ClinicalTrials.gov: NCT00491244).

**RESULTS**: Compared with monotherapy, combination therapy had a greater sustained virologic response rate (64% vs. 33%; relative risk, 1.92 [95% CI, 1.41 to 2.62]; P < 0.001). More patients receiving combination therapy had hemoglobin levels less than 8.5 g/dL than those receiving monotherapy (72% vs. 6%; risk difference, 66% [CI, 56% to 76%]; P < 0.001). Patients receiving combination therapy required a higher dosage (mean, 13 946 IU per week [SD, 6449] vs. 5833 IU per week [SD, 1169]; P = 0.006) and longer duration (mean, 29 weeks [SD, 9] vs. 18 weeks [SD, 7]; P = 0.004) of epoetin-β than patients receiving monotherapy. The adverse event-related withdrawal rates were 7% in the combination therapy group and 4% in the monotherapy group (risk difference, 3% [CI, -3% to 9%]).

**CONCLUSION**: In treatment-naive patients with HCV-1 receiving hemodialysis, combination therapy with pegylated interferon plus low-dose ribavirin achieved a greater sustained virologic response rate than pegylated interferon monotherapy.

3. Rodriguez-Torres, et al. Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment-naïve patients with HCV genotype 1: a randomized, 28-day, dose-ranging trial. J Hepatol. 2013 Apr;58(4):663-8. Epub 2012 Nov 23.

**BACKGROUND & AIMS**: Sofosbuvir (formerly GS-7977) is a pyrimidine nucleotide analog inhibitor of the hepatitis C virus (HCV) NS5B polymerase. We assessed the safety, tolerability, antiviral activity, and pharmacokinetics of sofosbuvir plus pegylated-interferon (PegIFN)/ribavirin (RBV) in a 28-day, dose-ranging trial in treatment-naïve patients infected with genotype 1 HCV.

**METHODS:** In this double-blind study, 64 patients were randomized (1:1:1:1) to receive one of three once-daily doses of oral sofosbuvir (100, 200, or 400mg) or placebo plus PegIFN/RBV for 28 days, after which all patients continued to receive PegIFN/RBV alone for a further 44 weeks.

**RESULTS:** Patients in the sofosbuvir/PegIFN/RBV groups experienced mean reductions in HCV RNA >5 $\log_{10}$ IU/ml (-5.3 for 100 mg, -5.1 for 200 mg and -5.3 for 400 mg) vs. -2.8 $\log_{10}$ IU/ml for placebo/PegIFN/RBV after 28 days. Rapid virologic response (RVR) rates were markedly higher after sofosbuvir treatment (88-94%) than placebo (21%), as were rates of sustained virologic response (SVR) at post-treatment Week 24 (56%, 83%, and 80% for sofosbuvir 100, 200, and 400 mg, respectively, vs. 43% for placebo). The number of patients experiencing virologic breakthrough and post-treatment relapse was higher in the sofosbuvir 100 mg group than sofosbuvir 200 and 400 mg groups. Sofosbuvir was well tolerated; the most frequent adverse events were fatigue and nausea.

**CONCLUSIONS:** These results support further studies with sofosbuvir at 200 mg and 400 mg to determine the optimal dose and treatment duration of sofosbuvir in HCV genotype 1

4. Benhamou et al. Telaprevir activity in treatment-naive patients infected hepatitis C virus genotype 4: a randomized trial. J Infect Dis. 2013 Sep;208(6):1000-7. Epub 2013 Jun 24.

**BACKGROUND:** This partially blinded, randomized, pha**se 2a C210 study evaluated the antiviral activity of telaprevir-based regimens in treatment-naive** patients with chronic hepatitis C virus (HCV) genotype 4 infection.

**METHODS:** Twenty-four patients received telaprevir 750 mg every 8 hours for 15 days (T; n = 8), telaprevir in combination with pegylated interferon alfa-2a and ribavirin (Peg-IFN/RBV) for 15 days (TPR; n = 8), or Peg-IFN/RBV plus placebo for 15 days (PR; n = 8), followed by Peg-IFN/RBV for 46 or 48 weeks. The primary objective was to assess the effect of telaprevir on HCV RNA levels.

**RESULTS:** HCV RNA levels decreased slightly with T and PR; TPR produced substantial, rapid declines. On day 15, median reductions in the HCV RNA load from baseline were -0.77, -4.32, and -1.58 log10 IU/mL for T, TPR, and PR, respectively, and 0 patients in the T group, 1 in the TPR group, and 0 in the PR group had undetectable HCV RNA. Five of 8 patients who received telaprevir monotherapy had viral breakthrough within 15 days of treatment. Adverse event incidence was similar across treatments and comparable with the incidences from previous clinical trials. One patient (in T group) had a serious adverse event (considered unrelated to telaprevir) that led to treatment discontinuation.

**CONCLUSIONS**: Telaprevir with Peg-IFN/RBV had greater activity than Peg-IFN/RBV treatment or telaprevir monotherapy against HCV genotype 4. Telaprevir was generally safe and well tolerated. Further investigation of telaprevir combination therapy in patients with HCV genotype 4 infection is warranted**.**