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Abbreviated Class Update: Hepatitis C

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

Last Review: March 2014
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:
- New guidelines recommend prioritization of HCV patients for treatment based on disease severity, including those patients with advanced fibrosis (METAVIR score F3 to F4) and in those patients with clinically significant extra-hepatic manifestations.[1,2]
- There remains insufficient evidence evaluating treatment with sofosbuvir or simeprevir in patients with decompensated cirrhosis. New guidelines recommend that those with decompensated cirrhosis not on a transplant waiting list should only be offered an interferon-free regimen within a clinical trial, an expanded access program or within experienced centers, because the efficacy and safety outcomes have not yet been established for this group.[3]
- There is new low quality evidence that simeprevir in combination with peginterferon alfa and ribavirin results in a higher SVR rate compared to peginterferon plus ribavirin dual therapy in GT1 chronic HCV patients, both treatment naïve and previous relapsers.[4,5]
- There remains insufficient evidence evaluating sofosbuvir in subpopulations and comorbidities including those with decompensated cirrhosis, HBV or HIV co-infection, treatment experienced patients, patients with alcohol or drug use within the past year, significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, and renal disease.[6]
- There is a lack of comparative evidence and evidence from randomized controlled trials evaluating the efficacy and long term safety of sofosbuvir in patients with genotype 1 HCV. New guidance from the National Institute for Health and Care Excellence and the German Institute for Quality and Efficiency in

Healthcare have concluded they cannot decide if sofosbuvir is a cost-effective use of resources, particularly in genotype 1 patients, until more comparative evidence is available.[7,8]

Recommendations:

- Recommend including additional changes to PA criteria based on Hepatitis C Advisory Committee Recommendations, including limiting approval to the following patient populations:
    - Patients with extrahepatic manifestations of HCV who have formal documentation from a relevant specialist that their condition is HCV related
    - HCV/HIV co-infected patients with cirrhosis
    - HCV infection in the transplant setting (approval needs to be cleared by the OHSU Liver Transplant Program)
    - Cirrhotic (stage 4) patients without ongoing progressive decompensation
- Exclude patients on marijuana as well as alcohol in the past 6 months.
- To determine if prescriber has adequate experience in hepatitis C, ask the question at the end of PA criteria, and perform outreach.

Previous Conclusions and Recommendations:

- 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. [9] 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%).[9]
- 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 low quality evidence that in genotypes 2 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.[10]
- 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.[10]
- 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.

Reason for Review: The evidence and clinical practice guidelines for the treatment of chronic Hepatitis C continues to evolve. New evidence, including systematic reviews and clinical guidelines, will be reviewed for further decision-making.

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Background:

Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma.[11] 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. [11] 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.[12] Relapse is defined as a patient achieving HCV RNA less than the lower limit of quantitation or the lower limit of detection at the last measurement on treatment but subsequently having a HCV RNA greater than or equal to the lower limit of quantitation or detection post treatment.[6]

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. [11] Current standard of care for Genotype 1 CHC is a protease inhibitor (boceprevir or telaprevir) plus pegylated interferon and ribavirin.[13] 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.[14]

Patients at greatest risk of progressing to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis (Metavir fibrosis stage 2 or greater). Patients with compensated cirrhosis are at risk of progressing to decompensation, hepatocellular carcinoma or death. The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver-related disease and prolonging graft survival in liver transplant recipients. Disease progression varies greatly among patients with compensated liver disease and the number needed to treat to prevent long term outcomes is dependent on the baseline risk for events. The newer costly treatments with high SVR rates will have the most benefit among patients at highest risk of cirrhosis-related events.[15]

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.[16] 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.[12] 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 February 2014 (since the most recent Hepatitis C Class Update) and ending June 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.

Systematic Reviews:

The Oregon Center for Evidence-based Policy recently evaluated sofosbuvir for the treatment of hepatitis C.[6] Ten studies were identified, as well as three studies cited in the FDA review which have not been published. Since the release of this report, the VALENCE trial has been published and is described in Table 3.[17] There was one placebo controlled trial and one study that compared sofosbuvir plus ribavirin to peginterferon plus ribavirin. These included patients with HCV genotypes 2 and 3. All other studies were designed to refine drug dose, drug combination or duration of treatment and did not include a control group. Studies included populations with favorable prognostic factors and only one study with HCV/HIV co-infected patients was identified. However, this study was from the FDA review and has not been published. All included studies were rated with a high risk of bias (poor quality) and only one study was rated as having fair applicability. Only one study had a comparator arm.

Response rates from the published studies, using SVR12, ranged from 10% to 89% for patients with HCV-1, 82% to 95% for HCV-2, and 30% to 84% for patients with HCV-3. [6] Relapse rates were not reported consistently and often only in per-protocol analyses. Rates ranged from 5% in treatment naïve genotype 2 patients treated with sofosbuvir plus ribavirin to 90% in treatment experienced genotype 1 patients. Only 6 studies tested one of the four FDA approved treatment regimens, shown below in table 1. The evidence for interferon-free treatment in genotype 1 comes from one study with only 60 patients. The genotype 2 regimen has the most supporting evidence with the sofosbuvir plus ribavirin 12 week regimen (n=1051; 4 trials). [6]

Table 1: FDA approved treatment regimens and response rates[6]

Genotype	Treatment	SVR12	Relapse	# of Studies (Study name)	Study N
HCV-1	SOF+PEG+RBV 12 w	89%	4% to 8.6%	2 (NEUTRINO, ATOMIC)	379
	SOF+RBV 24 w	68%	28%	1 (Osinusi, NIH Study)	60
HCV-2	SOF+RBV 12 w	82% to 95%	5% to 18%	4 (FISSION, FUSION, POSITRON, VALENCE)	1051
HCV-3	SOF+RBV 24 w	84%	14%	1 (VALENCE)	250

Overall, discontinuations of therapy due to adverse events were low in studies and the most common side effects were fatigue, anemia, nausea, rash, headache, insomnia, and pain. A total of 34 patients (2.6%) experienced a treatment-emergent, serious adverse event, with no significant patterns identified. Nonetheless, patients included in the studies were healthier than the general population and studies were small and of short duration. The authors state a potential bias in under-representing the true effect of adverse events and that larger and longer term studies are needed to better describe the harms profile of sofosbuvir. [6]

The authors also searched for ongoing trials through ClinicalTrials.gov. They found no studies which compare sofosbuvir-based treatment to the current standard of care, no evidence on sofosbuvir, interferon, and ribavirin treatment in genotype 1 patients who have failed previous treatment, and no studies conducted by other groups other than pharmaceutical companies. [6]

Who to Treat and When to Treat:
The authors comment that using the study inclusion and exclusion criteria might help select patients who are more likely to respond to treatment. Six studies excluded patients with cirrhosis, and in the studies including patients with cirrhosis, none had decompensated cirrhosis. Other exclusion criteria included HIV or HBV co-infection, significant alcohol or drug use within the past 12 months, excessive current alcohol use, significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, and significant renal disease.

The authors list the following factors to consider when developing treatment and coverage criteria: [6]

- Limit use to genotype 2 and 3, until comparative trials are available for genotype 1.
- Do not use sofosbuvir as monotherapy
- Limit use to patients who failed or did not tolerate current standard of care regimens or in whom peginterferon is contraindicated
- Confirm degree of liver fibrosis or cirrhosis prior to authorization of treatment
- Treat only patients at greatest risk of progressing to cirrhosis
- Consider use for patients with HIV or HBV co-infection or those post-liver transplant carefully until comparative trials are available.
- Exclude use in patients with alcohol or drug use within the past year, significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, renal disease

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- Ensure that patients who start therapy are closely tracked to optimize full treatment and follow-up, including prevention of re-infection

Clinical Guidelines:

World Health Organization (WHO)

In April 2014, the World Health Organization produced its first guidelines for the screening, care and treatment of persons with hepatitis C infection.[2,18] The guidelines are targeted primarily toward policy makers and physicians in low- and middle-income countries. Both sofosbuvir and simeprevir were given strong recommendations for use based on high quality evidence. It was recommended that sofosbuvir be given in combination with ribavirin with or without pegylated interferon in genotypes 1, 2, 3, and 4 HCV infections rather than pegylated interferon and ribavirin alone. Simeprevir is recommended for persons with genotype 1b HCV infection and for persons with genotype 1a HCV infection without the Q80K polymorphism rather than pegylated interferon and ribavirin alone. However, at the time, pricing information was not available so this was not taken into consideration of making the recommendations.

The guideline panel recommends that patients with advanced fibrosis and cirrhosis (METAVIR stages F3 and F4) should be prioritized for treatment as they are at higher risk of developing cirrhosis and hepatocellular carcinoma. If resources permit, then persons with less advanced fibrosis could also be considered for treatment.

EASL Clinical Practice Guidelines:

In April 2014, the European Association for the Study of the Liver (EASL) updated its HCV treatment guidelines.[1] 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. The guideline panel provides the following recommendations on who to treat:

- All treatment naïve and experienced patients with compensated chronic liver disease and who have no contraindications to treatment should be considered for therapy (A1 Recommendation).
- Those patients with advanced fibrosis (METAVIR score F3 to F4) and in those patients with clinically significant extra-hepatic manifestations should be prioritized for treatment (A1 Recommendation).
- For patients with minimal or no fibrosis, treatment may be deferred.
- Interferon-free treatment may also be considered in patients with decompensated cirrhosis, although limited data is available in this population. Patients on the transplant list should be considered (A1 Recommendation). Interferon-free treatment in patients with decompensated disease should only be attempted in experienced centers until further safety and efficacy date is available.
- Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection (A1 Recommendation).

Treatment of genotype 1 CHC:

Option 1:

- A combination of pegylated interferon, ribavirin, and sofosbuvir for 12 weeks is recommended (A1 recommendation)

Option 2:

- A combination of pegylated interferon, ribavirin, and simeprevir for 12 weeks (A1 Recommendation).

Option 3:

- Patients with HCV genotype 1, subtype 1b can be treated with pegylated interferon, ribavirin, and daclatasvir for 24 weeks (Recommendation B1).

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Interferon-intolerant or –ineligible

- Ribavirin and sofosbuvir for 24 weeks (Recommendation B2). This should be proposed when no other interferon-free option is available.
- Patients can be treated with sofosbuvir and simeprevir for 12 weeks (Recommendation B1). Ribavirin should be considered in patients with predictors of poor response, especially prior non-responders and/or patients with cirrhosis.
- Combination of sofosbuvir and daclatasvir for 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients (Recommendation B1). Ribavirin should be considered in patients with predictors of poor response, especially prior non-responders and/or patients with cirrhosis.

Treatment of genotype 2 CHC:

- The combination of sofosbuvir and ribavirin for 12 weeks is recommended. In settings where this is not an option, the combination of pegylated interferon and ribavirin remains acceptable.
- Cirrhotics and/or treatment-experienced patients could be treated with pegylated interferon and ribavirin and sofosbuvir for 12 weeks.

Treatment of genotype 3 CHC:

- The combination of pegylated interferon, ribavirin, and daily sofosbuvir for 12 weeks appears to be more effective than 24 weeks of the combination of sofosbuvir and ribavirin, which should be option 2. (Recommendation A2). This therapy (sofosbuvir plus ribavirin for 24 weeks) is suboptimal in treatment-experienced cirrhotics, who should be proposed an alternative treatment option.
- Patients can be treated with an interferon-free combination of daily sofosbuvir and daily daclatasvir for 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients as option 3 (Recommendation B1). Adding daily ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.

Monitoring:

- A real-time PCR-based assay with a lower limit of detection of <15 IU/ml should be used to monitor HCV RNA levels during and after therapy.
- For patients on the combination of pegylated interferon, ribavirin, and sofosbuvir, HCV RNA should be measured at baseline and at weeks 4, 12, and 12 or 24 weeks after the end of therapy (Recommendation A2).
- In patients treated with an interferon-free regimen, HCV RNA should be measured at baseline, week 2(assessment of adherence), week 4, week 12 or 24, and 12 or 24 weeks after the end of therapy.
- Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on people who inject drugs, or men who have sex with men with on-going risk behavior

Liver Transplant:

- Patients with decompensated cirrhosis awaiting liver transplantation (Child-Pugh B and C) can be treated with daily ribavirin and sofosbuvir until liver transplantation in experienced centers under close monitoring.
- In patients treated with an interferon-free regimen, HCV RNA should be measured at baseline, week 2(assessment of adherence), week 4, week 12 or 24, and 12 or 24 weeks after the end of therapy.
- Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on people who inject drugs, or men who have sex with men with on-going risk behavior

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- Patients with decompensated cirrhosis not on a transplant waiting list should only be offered an interferon-free regimen within a clinical trial, an expanded access program or within experienced centers, because the efficacy and safety outcomes have not yet been established for this group (Recommendation B1).

Co-Morbidities:

- Patients who inject drugs should be considered for HCV treatment on an individualized basis and delivered within a multidisciplinary team setting (Recommendation A1).
- Pre-Therapeutic assessment should include an evaluation of housing, education, cultural issues, social functioning and support, finances, nutrition, and drug and alcohol use. Patients who inject drugs should be linked into social support services and peer report.
- Drug and alcohol users or any other patients with ongoing social issues or history of psychiatric disease are at risk of lower adherence and reduced likelihood of achieving SVR. They need to be monitored more closely during therapy and need more intensive multidisciplinary support (Recommendation B1).

Federal Bureau of Prisons:

The Federal Bureau of Prisons released interim guidance for the management of Chronic HCV infection in May 2014.[19] They provide the following groups that should be prioritized for treatment:

- Advanced hepatic fibrosis/cirrhosis
- Liver transplant recipients
- HIV co-infection
- Comorbid medical conditions associated with HCV (cryoglobulinemia and certain types of lymphomas)
- Continuity of care for newly incarcerated inmates who are being treated at the time of incarceration

National Institute for Health and Care Excellence (NICE):

In draft recommendations, NICE is asking for more information on sofosbuvir for the treatment of chronic hepatitis C.[7] Draft guidance states that available evidence demonstrates that sofosbuvir is effective in certain patients; however, evidence is lacking in subgroup populations and there are substantial uncertainties. Without further information, they cannot decide if sofosbuvir is a cost-effective use of resources. The committee concluded the following:

- Recommends further analysis comparing sofosbuvir in combination with ribavirin, with or without peginterferon alfa compared with peginterferon alfa and ribavirin in genotype 1 and genotype 3 CHC.

Institute for Quality and Efficiency in Health care (IQWiG**):**

The IQWiG, the German equivalent of NICE, released a preliminary report on the effectiveness of sofosbuvir.[8] Due to the lack of comparative studies, IQWiG concluded that there was insufficient evidence to assess effectiveness of treatment in genotype 1 and genotypes 3-6. The guideline found a positive effect of sofosbuvir treatment in genotype 2 based on one comparative study, but insufficient evidence to conclude that sofosbuvir had a better harms profile. The FISSION trial compared 12 weeks of sofosbuvir plus ribavirin to 24 weeks of peginterferon alfa plus ribavirin. Overall, they assessed the risk of bias of this study as high.

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Department of Veterans Affairs (VA)

The VA National Hepatitis C Resource Center Program released treatment considerations for Chronic HCV earlier in 2014.[3] The purpose of this was to provide a detailed algorithmic approach to assist in clinical decision-making based on specific patient characteristics. For considerations for selecting patients for treatment, the guideline gave the highest strength of evidence to patients with: hepatocellular carcinoma, post-transplant recipients with cirrhosis, and for carefully evaluating treatment in patients with decompensated cirrhosis. It is recommended that some patients be deferred treatment, including those without cirrhosis. They recommend that patients with severe mental health conditions should be considered for therapy on a case-by-case basis and all patients should be evaluated for current alcohol and other substance use. Patients with active substance or alcohol-use disorders should be considered for therapy on a case-by-case basis.

The VA also includes the following criteria to use to determine whether a patient is interferon ineligible or intolerant:

- Platelet count <75,000/mm3
- Decompensated liver cirrhosis (Child-Turcotte-Pugh Class B or C, CTP score ≥ 7)
- Severe mental health conditions that may be exacerbated by interferon or respond poorly to medical therapy
- Autoimmune diseases that may be exacerbated by interferon
- Inability to complete a prior treatment course due to documented interferon-related adverse effects

Lastly, the VA provides laboratory monitoring recommendations. They recommend that patients should have HCV RNA assessed at week 4 of treatment. If the HCV RNA is detectable at week 4 or any time point thereafter, reassess in 2 weeks. If HCV RNA increases at any time point or if the 8-week level remains detectable, discontinuation of all treatment should be strongly considered (Strong recommendation; expert opinion).

UK Consensus Guidelines

New 2014 expert UK guidelines were developed to provide clinicians with an expert opinion of the current best standard of care.[20] The panel group consisted of members of leading hepatology and infectious disease societies. All but one of the 16 authors disclosed personal relationships with pharmaceutical companies and funding came from 13 pharmaceutical companies, adding risk of bias to the recommendations. Both published studies and unpublished studies from abstract presentations were included. Overall, 25 of the 26 treatment recommendations include the newer agents' sofosbuvir and simeprevir. Recommendations also include faldaprevir, which is not yet approved in the US. The costs and pricing structures was not taken into account and it was assumed that these drugs were deemed cost effective for NHS use by Scottish Medicines Consortium (SMC) and NICE. After this, NICE did not conclude that it was cost effective until further data was released. The following table provides a summary of the recommendations from the UK guidelines. There was no grading of the evidence or strength of the recommendation given, reiterating that these are meant to be expert opinion and are not necessarily evidence-based. No preference was given to one regimen over another, stating that each is a viable option.

Table 2: Summary of Recommendation from UK expert guidelines

Genotype	Treatment naïve	Treatment experienced	Cirrhosis or severe fibrosis
1a	12 weeks SOF + PR 12 week SMF, 24 weeks PR 12 weeks FDV, 24 weeks PR	12 weeks SMV, 24 or 28 weeks PR (RGT) 12 weeks SOF and PR	12 weeks SOF and PR

1b	12 weeks SOF and PR 12 weeks SMV, 24 weeks PR 12 weeks FDV, 24 weeks PR	12 weeks SMV, 24 or 48 weeks PR (RGT) 12 weeks SOF and PR	
2	12 weeks SOF and RBV	12 weeks SOF and RBV	12 weeks SOF and RBV
3	12 weeks SOF and PR 24 weeks PR 24 weeks SOF and RBV	12 weeks SOF and PR 24 weeks SOF and RBV	24 weeks SOF and RBV
4,5,6	12 weeks SOF and PR 12 weeks SMV, 24 or 48 weeks PR (RGT)	12 weeks SOF and PR 12 weeks SMV, 24 or 48 weeks PR (RGT)	12 weeks SOF and PR
SOF: sofosbuvir; SMV: simeprevir, PR: pegylated interferon and ribavirin, FDV: faldaprevir, RGT: response guided therapy, RBV: ribavirin			

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.[10] 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. SVR 12 rates from the COSMOS trial are shown below in table 2.

Table3: SVR12 Results from Cosmos Trial[6]

COSMOS SVR12 Results Presented at AASLD and EASL Conferences					
Cohort	**Citation**	**SOF + SMV 12 weeks**	**SOF+SMV+RBV 12 weeks**	**SOF + SMV 24 weeks**	**SOF+SMV+RBV 24 weeks**
1	AASLD 2013 (Jacobson 2013b)	92.9% (13/14)	96.3% (26/27)	100% (14/14)	79.2% (19/24)
	EASL 2014 (Sulkowski 2014)	92.9% (13/14)	96.3% (26/27)	100% (13/13)	90.5% (19/21)
2	EASL 2014 (Lawitz 2014)	92.9% (13/14)	92.6% (25/27)	100% (16/16)	93.3% (28/30)

Randomized Controlled Trials:

Seven potentially relevant RCTs were evaluated from the literature search. After further review, 4 RCTs[21–24] included drugs not yet FDA approved and were therefore excluded. The remaining 3 RCTs are briefly described in the table below.

Table 4: Description of RCTs

Study	Comparison	Population	Primary Outcome	Results	Study Quality

Zeuzem et al.[17] VALENCE RCT, phase III, open-label, no placebo group or comparator	Sofosbuvir plus ribavirin (24 weeks for genotype 3 and 12 weeks for genotype 2).	HCV genotype 2 and 3, tx experienced or tx naïve; up to 20% with cirrhosis, HCV RNA > 10,000 IU/ml'(n=419)' 41% women 21% cirrhosis 58% previously treated, of whom 30% had no response	SVR12	<u>SVR12</u> GT2: 68/73, 93% (85 to 98%) * GT3: 213/250, 85% (82 to 91%)** *All 68 patients maintained SVR at week 24 **206 (96.7%) maintained SVR at week 24 -Lowest response rate in GT 3 previously treated patients with cirrhosis (62%) <u>Relapse:</u> GT2: 5/73 (7%) GT3: 33/250 (13%)	<u>Poor</u> • Descriptive, open-label study with no placebo group, comparator, or hypothesis testing • Revised study design resulted in no formal statistical comparisons • Small number of patients with characteristics associated with a poor response rate
Manns, et al.[5] QUEST-2 Phase III, RCT, DB, PC	Simeprevir vs. placebo, both in combination with peginterferon alfa plus ribavirin	Treatment naïve, GT1 patients Decompensated cirrhosis, HIV, HBV were excluded (n=391)	SVR12	<u>SVR12</u> SMV: 209/257 (81%) Pla: 67/134 (50%) P<0.0001 <u>Relapse:</u> SMV: 30/236 (13%) Pla: 21/88 (24%)	<u>Fair</u> • Randomized and concealment of allocation using computer-generated randomization schedule and interactive voice response system • Patients and investigators blinded • Higher withdraw in placebo group than tx (12.6% vs. 4.7%)
Forns, et al.[4] RCT, DB, PC, phase III	Simeprevir vs. placebo, both in combination with peginterferon alfa plus ribavirin	HCV GT 1 patients who had relapsed after 24 weeks or more of interferon based therapy (n=393)	SVR12	<u>SVR12</u> SMV: 206/260 (79.2%) Pla: 48/133 (36.1%) P<0.001 <u>Relapse:</u> SMV: 46/249 (18.5%) Pla: 45/93 (48.4%)	<u>Fair</u> • Centrally randomized; unclear allocation concealment • Patients blinded investigators blinded up to week 72 • Outcome assessors unblinded

<u>Ongoing Trials:</u>

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.[9]

Authors: Megan Herink, Pharm.D.

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Appendix 1: Prior authorization Criteria

Sofosbuvir (Sovaldi®)

Goal(s) :

- Approve 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. What diagnosis is being treated?	**Record ICD9 code**	
2. Is this an OHP covered diagnosis?	**Yes:** Go to #3	**No:** Pass to RPH; Deny (Not covered by the OHP)
3. Is the request for treatment of Chronic Hepatitis C?	**Yes:** Go to #4	**No:** Pass to RPh, Deny For Appropriateness
4. Is the request for continuation of therapy?	**Yes:** Go to "Continuation of Therapy"	**No:** Go to #5
5. Is the medication being prescribed by or in consultation with a ~~specialist in the field of gastroenterology, infectious disease, or hepatitis C~~ hepatologist?	**Yes:** Go to #6	**No:** Pass to RPh, Deny For Appropriateness
6. 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 #7
7. 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). 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 #8	**No:** Pass to RPh, Deny For Appropriateness
8. Does the patient have a HIV coinfection?	**Yes:** Go to #9	**No:** Go to #10
9. Is the patient under the supervision of an HIV specialist?	**Yes:** Go to #10	**No:** Pass to RPh; Deny (medical appropriateness)
10. If applicable, has the patient been abstinent from IV drug use, marijuana or	**Yes**: Go to #11	**No:** Pass to RPh, Deny for

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alcohol abuse for ≥ 6 months?		appropriateness
11. 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 #12
12. What Hepatitis C genotype is the patient? Record Genotype:	Record Genotype and go to #13	
13. Does the patient have genotype 1 or 4 chronic hepatitis C?	**Yes:** Go to # 14	**No:** Go to #17
14. Is the medication being used as triple therapy with both ribavirin and peginterferon alfa and meets criteria for pegylated interferon-alfa and ribavirin?	**Yes:** Approve for 12 weeks total therapy	**No:** Go to #15
15. Is the medication being used with ribavirin or simeprevir?	**Yes:** Go to #16	**No:** Pass To Rph; Deny for Appropriateness
16. Is the patient interferon ineligible defined by having one of the following conditions: • Previous adverse reaction or hypersensitivity to interferon • Decompensated liver disease • Severe or uncontrolled psychiatric disorder in consult with a psychiatrist • Autoimmune hepatitis or other autoimmune disorders • Unstable cardiac disease 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
17. Does the patient have genotype 2 chronic hepatitis C?	**Yes:** Go to #18	**No:** Go to #19
18. Is the medication being used with ribavirin?	**Yes:** Approve for 12 weeks total therapy	**No:** Pass To Rph; Deny for Appropriateness
19. Does the patient have genotype 3 chronic hepatitis C?	**Yes:** Go to #20	**No:** Pass To Rph; Deny for Appropriateness
20. Is the medication being used with both ribavirin and peginterferon alfa and meets criteria for pegylated interferon-alfa and ribavirin?	**Yes:** Approve for 12 weeks total therapy	**No:** Go to #21
21. 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

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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). If patient is awaiting liver transplantation, approve for up to additional 24 weeks or until liver transplantation, whichever occurs first.	**No:** DENY (Medical Appropriateness)

Dosage and Administration:

Genotype 1 and 4	Sofosbuvir + peginterferon alfa + ribavirin	12 weeks
Genotype 2	Sofosbuvir + ribavirin	12 weeks
Genotype 3*	Sofosbuvir + ribavirin	24 weeks
Genotype 1 and interferon ineligible	Sofosbuvir + ribavirin	24 weeks
Those with hepatocellular carcinoma awaiting liver transplantation	Sofosbuvir + ribavirin	Up to 48 weeks or until ilver transplantation, whichever occurs first

*Certain patients with genotype 3 (nonresponders with advanced fibrosis) can also be treated with sofosbuvir + peginterferon alfa + ribavirin for 12 weeks if deemed appropriate by physician

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P&T Board Action: 1/30/13 (MH)
Revision(s): 3/27/13, 7/31/14
Initiated:

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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? Document appropriate ICD9 code:	**Yes:** Go to #2	**No:** Pass to RPh, Deny For Appropriateness
2. Does the patient have documented HCV genotype 1? 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	**Yes:** Go to #11	**No:** Pass to RPh, Deny For

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have documented compliance/adherence to their previous treatment?		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: • 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 (Medical Appropriateness) 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: • 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 (Medical Appropriateness) 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

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		Treatment Week 24.
3. Is the patient a prior partial or null responder?	**Yes:** Approve as follows: • 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 (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: • 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 (Medical Appropriateness) 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** 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) Week 24: Detectable Discontinue peginterferon and ribavirin. 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: • Approve additional 14 weeks of boceprevir for total treatment duration of 28 weeks (4 week lead-in, 24 weeks triple therapy)	**No:** DENY (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: • 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 (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: • Approve additional 22 weeks of boceprevir for total treatment duration of 36 weeks (4 week lead-in, 32 weeks triple therapy)	**No:** DENY (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: • 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 (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: • Continue triple therapy with boceprevir for a total treatment duration of 48 weeks (4 week lead-in, 44 weeks triple therapy).	**No:** DENY (Medical Appropriateness)

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***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.

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: • 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 (Medical Appropriateness) 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: • 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 (Medical Appropriateness) 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.		

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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? Message: - 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? Document appropriate ICD9 code: (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?	**Yes:** Forward to DMAP Medical Director	**No:** Go to #7

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Verify by reviewing member's Rx profile for PEG-Intron or Pegasys, PLUS ribavirin history. Does not include prior treatment with interferon monotherapy or non-pegylated interferon.		
7. Does the patient have any of the following contraindications to the use of interferon-ribavirin therapy? • severe or uncontrolled psychiatric disorder • decompensated cirrhosis or hepatic encephalopathy • hemoglobinopathy • untreated hyperthyroidism • severe renal impairment or transplant • autoimmune disease • pregnancy • 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? 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. 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) Recommend: LAMIVUDINE (EPIVIR HBV) ADEFOVIR (HEPSERA)	**No:** Approve Pegasys #4 x 1ml vials or #4 x 0.5 ml syringes per month for 12 months (maximum per lifetime).

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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.	**No:** DENY (Medical Appropriateness) Treatment with pegylated interferon-ribarvirin does not meet medical necessity criteria because there is poor chance of achieving an SVR.

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).

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.
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Stage is indicative of fibrosis:			**Grade is indicative of necrosis:**	
Stage 0	No fibrosis			

Authors: Megan Herink, Pharm.D.

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