The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection

An Action Guide for the Treatment of Chronic Hepatitis C Infection: Next Steps for Payers and Policymakers

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Completed by:

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Introduction

About This Guide

Evidence from clinical research, which informs effectiveness reviews, provides a critical foundation for judgments that patients, clinicians, and health insurers must make about treatment choices and coverage policies. Yet that evidence is often not translated in a way that is helpful to inform health care decisions. This document is a companion policy guide designed to help patients, clinicians, and insurers make use of the results of a recent technology assessment entitled "*The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection*" developed by the Institute for Clinical and Economic Review (ICER) and faculty at University of California San Francisco. This report formed the basis for the deliberations and votes of the California Technology Assessment Forum (CTAF) Panel – an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy, who evaluate evidence and vote on the comparative clinical effectiveness and value of medical interventions. All CTAF Panel members meet strict conflict of interest policies.

CTAF held its public meeting on new treatments for hepatitis C on March 10, 2014 in San Francisco, California. A full report summarizing the discussion and votes taken is available on the CTAF website. We have developed this Action Guide to provide a user-friendly overview of the CTAF findings and an associated list of specific evidence-based action steps that patients, clinicians, and insurers can take to improve patient outcomes and the overall value of treating hepatitis C. The content provided here is for informational purposes only, and it is not designed to replace professional medical advice.

A Note on CTAF Evidence Voting

Each public meeting of CTAF involves deliberation and voting on key questions on the comparative clinical effectiveness and value of the various diagnosis and treatment options discussed. When voting on economic impact, CTAF Panel members are not provided with prescribed thresholds or boundaries for how to interpret value. Rather, the CTAF Panel members are asked to assume the perspective of a state Medicaid program or a provider organization making resource allocation decisions within a relatively fixed budget.

Executive Summary

This assessment for the California Technology Assessment Forum (CTAF) evaluates the evidence on the comparative clinical effectiveness and value of two drugs recently approved by the FDA for the treatment of chronic hepatitis C: simeprevir and sofosbuvir. Chronic hepatitis C is a common infection that is a major cause of chronic liver disease, liver failure, and hepatocellular carcinoma, and it is the leading indication for liver transplantation in the Western world.[1] Prior to 2011, the combination of pegylated interferon and ribavirin (PR) was the gold standard of therapy for the treatment of chronic hepatitis C. Approximately half of patients with genotype 1, the most prevalent type of hepatitis C in the US, could expect with PR therapy to clear the virus from their bloodstream entirely and maintain a sustained virologic response (SVR) 24 weeks after the end of treatment. PR therapy can be difficult, however, as both interferon and ribavirin can produce bothersome side effects, and in some cases, dangerous levels of anemia, neutropenia, and/or thrombocytopenia.[2] The 2011 introduction of first generation direct-acting antiviral (DAA) protease inhibitors boceprevir (Victrelis®, Merck & Co.) and telaprevir (Incivek®, Vertex Pharmaceuticals, Inc.) resulted in substantially improved SVR rates in many patients when used with PR regimens. This improvement has come with new challenges, however, including significant additional side effects and drug-drug interactions as well as stringent dosing requirements and high pill burdens for patients.[3]

Novel DAA agents have been developed with the potential for simplified dosing, fewer side effects and drug-drug interactions, and in some patients, the promise of interferon- and/or ribavirin-free treatment, particularly for genotypes 2 and 3 (the other common genotypes in the US). These new agents include the recently-approved second generation protease inhibitor simeprevir (Olysio®, Janssen Products, LP) and polymerase inhibitor sofosbuvir (Sovaldi™, Gilead Sciences, Inc.), as well as several other agents that are currently in late-stage clinical trials. Uncertainties remain with these new agents, however, as data on treatment-related side effects and their performance in particular patient populations are still emerging in the published literature. In addition, the costs of treatment are likely to increase substantially, with the two new agents expected to cost approximately $70,000 and $170,000 per course of therapy, depending on the duration of therapy.[4,5] Accordingly, the California Technology Assessment Forum has chosen to review the evidence on the comparative clinical effectiveness and comparative value of new DAA agents for chronic hepatitis C in relation to the existing standard of care in multiple patient populations.

This assessment will address the following questions: 1) among patients with genotype 1, are treatment regimens incorporating simeprevir and sofosbuvir equivalent or superior to the previous standard of care: pegylated interferon plus ribavirin and one of the first generation protease inhibitors telaprevir or boceprevir; 2) among patients with genotypes 2 and 3, is the combination of sofosbuvir and ribavirin equivalent or superior to the previous 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. The purpose of this assessment is to help patients, providers, and payers address these important questions and to support dialogue needed for successful action to improve the quality and value of health care for patients with hepatitis C.

Methods

The lack of head-to-head trials makes it difficult to assess the relative efficacy of the different drug regimens. In order to assess the relative efficacy of various treatment options, we performed a network meta-analysis, a form of indirect comparison that synthesizes direct and indirect evidence in a network of clinical trials to compare multiple interventions for the same indication. Network meta-analysis allows for indirect comparisons between therapies as long as they have the same type of control group (often placebo) in randomized trials.

To examine the potential clinical and economic impact of the introduction of sofosbuvir and simeprevir in California, we also developed a cohort model that assessed these effects over time horizons of one year, five years, and 20 years. Our model examined outcomes in different hypothetical cohorts of chronic hepatitis C patients organized by genotype, prior treatment status (i.e., treatment-naïve versus treatment-experienced), and eligibility for interferon therapy. Within each of these strata, outcomes and costs were assessed for a cohort of 1,000 hypothetical patients, age 60 years. We focused on genotypes 1, 2, and 3, as these represent over 97% of the hepatitis C population in the US.

Results

Genotype 1

Table ES1 on the next page summarizes the key benefits and harms for the treatment options for genotype 1. Among treatment-naïve patients, the first generation protease inhibitors increase the SVR at 12 weeks (SVR12) from the 40% range with PR to the 70% range. However, a large number of pills have to be taken about every 8 hours, and there are burdensome new side effects. These include a marked increase in anemia, with nearly 50% of patients taking telaprevir requiring erythropoietin stimulating agents for a median of 15 weeks during the course of treatment. Also common were nausea for both boceprevir and telaprevir, 20% more patients experiencing taste disturbance for boceprevir, and 20% more patients experiencing generalized pruritus with telaprevir. The drugs also have a large number of important drug interactions. Despite these problems, triple therapy with one of the two first generation protease inhibitors and PR was considered the standard of care for treatment of genotype 1 until the approval of simeprevir and sofosbuvir.

Table ES1. Summary of Benefits and Harms for Genotype 1 by Prior Treatment Status and Interferon Eligibility.

Treatment Approach (weeks)	SVR12 (Percent)	Treatment Burden	Adverse effects	Interferon -ineligible
Genotype 1				
Treatment-naïve				
PR (48)	47	48 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (≤ 30%)	No
BOC(24) + PR(48)	73	Add Q8 pills	Anemia (≤ 50%), more nausea and dysguesia, drug interactions	No
TVR(12) + PR(48)	74	Add Q8 pills	Anemia (≤ 50%), more nausea and pruritus, drug interactions	No
SMV(12) + PR(24-48)*	84	Add 1 pill to PR	No increase in anemia	No
SOF(12) + PR(12)	83	Add 1 pill to PR Fewer weeks	No increase in anemia	No
SMV(12) + SOF(12)	No data (Likely >90)	No P, maybe no R	Not reported yet	Maybe
Treatment-experienced				No
PR (48)	22	48 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
BOC(24) + PR(48)	64	Add Q8 pills	Anemia (≤ 50%), more nausea and dysguesia, drug interactions	No
TVR(12) + PR(48)	70	Add Q8 pills	Anemia (≤ 50%), more nausea and pruritus, drug interactions	No
SMV(12) + PR(24-48)*	70	Add 1 pill to PR	No increase in anemia	No
SOF(12) + PR(12)	No data (FDA estimate 71)	Add 1 pill to PR Fewer weeks	No increase in anemia	Maybe
SMV(12) + SOF(12)	90	No P, maybe no R	Not reported yet	Yes

Abbreviations: Q8 = taken every 8 hours; P = pegylated interferon; R = ribavirin

* Excluding patients with the Q80K mutation (approximately 10-15% of genotype 1 patients)

Among patients without the Q80k polymorphism, simeprevir appears to significantly improve the SVR12 compared with triple therapy. Additional benefits of simeprevir are reductions in the incidence of anemia and the pill burden for patients: simeprevir requires only one pill per day. It should be noted, however, that there are no published data from head-to-head trials of simeprevir and either of the first generation protease inhibitors, nor are there data on the impact of treatment on important long term patient outcomes such as the incidence of cirrhosis, liver decompensation, hepatocellular carcinoma, transplant, or death. Adverse events (AEs) specifically associated with simeprevir include pruritus, photosensitivity-induced rashes, and hyperbilirubinemia, but these are generally not severe and are easily managed.

Sofosbuvir plus PR also appears to cause less anemia and certainly represents a lower pill burden than standard triple therapy. It also requires only 12 weeks of PR rather than the 24 to 48 weeks

with the first generation protease inhibitors. Simeprevir plus PR in patients without the Q80K polymorphism and sofosbuvir plus PR appear to have very similar SVR12 rates for genotype 1 patients who are treatment-naïve or treatment-experienced. Most of the data for sofosbuvir, however, come from uncontrolled studies. Because of the shorter course of PR, sofosbuvir + PR has fewer severe/life-threatening (grade 3 and 4) AEs and fewer patients discontinuing treatment due to AEs, with no consistent pattern of an increase in AEs other than anemia (23% versus 14% for PR). As with simeprevir, this combination cannot be used in patients who are interferon-ineligible, and there are no long-term outcome data.

The preliminary data on simeprevir plus sofosbuvir (an off-label use not indicated by the FDA) with or without ribavirin come from uncontrolled trials and should be considered preliminary at this point but are nonetheless encouraging. The available data for treatment-experienced patients shows SVR12 rates averaging 90%; the SVR12 of treatment-naïve patients should be even better. This regimen is interferon-free, so can be used in interferon-ineligible patients. Since it is interferon-free (and perhaps ribavirin-free), simeprevir plus sofosbuvir should have markedly lower adverse event rates than regimens including PR.

Genotype 2

The story is more straightforward for genotype 2 (see Table ES2 on the next page). The combination of sofosbuvir plus ribavirin is superior in clinical effectiveness to prior standard treatment options. Among treatment-naïve patients, there was a large increase in SVR12 seen in the randomized FISSION trial and supported by the non-randomized VALENCE trial. The SVR12 for treatment-experienced patients was 86% and 90% in the two uncontrolled studies, but it was high enough to assume at least non-inferiority to PR therapy. The sofosbuvir-based regimen is interferon-free, which decreases grade 3 and 4 AEs, markedly decreases patients discontinuing therapy because of AEs, and reduces interferon-associated AEs such as fatigue, fever, myalgias, and headaches. Sofosbuvir therapy does not come with an increase in the anemia seen with the first generation protease inhibitors – in fact the incidence of anemia was lower in the sofosbuvir arms of the trials. The treatment course is also half as long (12 versus 24 weeks). Since the sofosbuvir-based regimen is interferon-free, the benefits should be even greater in those genotype 2 patients who are treatment-naïve but ineligible for interferon because of psychiatric or other co-morbidities. In the POSITRON trial, the SVR12 was 93% compared to 0% for treatment-naïve patients and 76% versus 0% for treatment-experienced patients.

Table ES2. Summary of Benefits and Harms for Genotype 2 by Prior Treatment Status and Interferon Eligibility.

Treatment Approach (weeks)	SVR12 (Percent)	Treatment Burden	Adverse effects	Interferon-ineligible
Genotype 2				
Treatment-naïve				
PR (24)	78	24 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
SOF(12) + R(12)	97	Shorter, no P	Less fatigue, less anemia	Yes
Treatment-experienced				
PR (24)	No data	24 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
SOF(12) + R(12)	88	Shorter, no P	Less fatigue, less anemia	Yes

Abbreviations: P = pegylated interferon; R = ribavirin

Genotype 3

The story is more complex for genotype 3 (see Table ES3 on the next page). For interferon-eligible patients, the existing randomized trial data do not demonstrate the superiority of sofosbuvir + PR to PR alone. Among treatment-naïve patients in the genotype 3 subgroup of the randomized phase 3 FISSION trial, 12 weeks of sofosbuvir plus ribavirin had a lower SVR12 than 24 weeks of PR (56% versus 62%). The SVR12 of the same regimen in the genotype 3 subgroup of the POSITRON study was similarly low at 61%. Given the poor outcomes at 12 weeks, the uncontrolled VALENCE study examined longer treatment courses, and the SVR consistently increased with increasing lengths of therapy to 16 and 24 weeks (56% to 93%). Similarly, the VALENCE study also showed that the SVR for treatment-experienced patients increased from 12 weeks (30%) to 16 weeks (62%) to 24 weeks (77%). These results should be confirmed in a second trial, but they formed the basis for the FDA approved regimen of 24 weeks of sofosbuvir for patients with genotype 3. The FDA approval also took into account that the sofosbuvir-based regimen is interferon-free, which decreases grade 3 and 4 AEs, markedly decreases patients discontinuing therapy because of AEs, and reduces interferon-associated AEs such as fatigue, fever, myalgias, and headaches. The treatment course is the same length as PR but without the injections and side effects of interferon. Since the sofosbuvir-based regimen is interferon-free, the benefits should be even greater in those genotype 3 patients who are treatment-naïve but ineligible for interferon because of psychiatric or other co-morbidities. In the POSITRON trial, the SVR12 was 61% compared to 0% for treatment-naïve patients and 76% versus 0% for treatment-experienced patients.

Table ES3. Summary of Benefits and Harms for Genotype 3 by Prior Treatment Status and Interferon Eligibility.

Treatment Approach (weeks)	SVR12 (Percent)	Treatment Burden	Adverse effects	Interferon-ineligible
Genotype 3				
Treatment-naïve				
PR (24)	62	24 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
SOF(24) + R(24)	93	Shorter, no P	Less fatigue, less anemia	Yes
Treatment-experienced				
PR (24)	No data	24 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
SOF(24) + R(24)	77	Shorter, no P	Less fatigue, less anemia	Yes

Abbreviations: P = pegylated interferon; R = ribavirin

Model Results Evaluating Clinical and Economic Outcomes of Hepatitis C Treatment Scenarios

Consistent with the findings of our systematic review and network meta-analysis, our model demonstrates that therapeutic regimens containing simeprevir or sofosbuvir have the potential to substantially increase the number of patients achieving SVR relative to previous therapeutic options, and sofosbuvir also provides the first effective interferon-free option for patients ineligible or intolerant to interferon.

For many patient subpopulations, however, the benefits of sofosbuvir and simeprevir come at a substantially increased cost. The costs for initial treatment regimens including sofosbuvir or simeprevir are expected to range from a low of approximately $88,000 to a high exceeding $175,000 per patient, depending on the drugs selected and the duration of initial treatment. Many patients who are treated with an initial course and who fail to achieve a prolonged SVR would likely be retreated, adding further to the estimated treatment costs over a one-year time frame.

For many comparisons with the previous standard of care, we estimate that the incremental cost required to achieve one additional SVR with newer treatment regimens is greater than $300,000. While the "cost per additional SVR" is not a common measure of cost-effectiveness in the literature, the costs per SVR generated in this analysis are generally higher than those previously published for telaprevir versus PR ($189,000),[8] alternative regimens of PR versus standard PR therapy ($17,000-$24,000),[9] and even highly active antiretroviral therapy in HIV patients ($1,000-$79,000).[10]

The clinical advantages of newer treatment regimens would therefore come with a substantial potential impact on health care budgets should a large number of patients be treated. As estimated by our model, we anticipate the average increase in treatment costs to be approximately $70,000 per patient for the newer agents. For example, in an employer-sponsored group health plan with 1 million enrollees, with an assumed underlying infection rate of 1.7%, there would be approximately 17,000 patients in this population infected with hepatitis C. If even 50% of this population comes forward for treatment, the immediate one-year budget impact for the plan would be estimated to be nearly $600 million, or approximately $50 on a per member, per month basis. It would be impossible for this magnitude of immediate increased spending to be accommodated within the budgets established by current health care premium structures, provider risk-sharing contracts, and patient co-payments.

Using an estimate that 50% of infected individuals in California would know of their infection and would be considered for treatment, we estimate that replacing current care with simeprevir and sofosbuvir-based regimens would raise drug expenditures by $22 billion in a single year. We looked for potential cost offsets to drug treatment resulting from downstream reductions in liver-related complications that would be expected with successful treatment of hepatitis C infection. For every 1,000 patients treated, our model estimated that switching from previous standard treatments to the most effective new regimens in all patients would prevent 18 liver-related events over five years and 70 events over 20 years. At a 5-year time horizon, however, cost offsets would still be estimated to represent less than 10-20% of upfront treatment costs. Even at a 20-year horizon, if all patients infected with hepatitis C are treated with the new regimens, the cost offset will only cover approximately three-quarters of initial drug costs.

The budget impact and cost offset figures change substantially under our second treatment scenario in which only patients with advanced liver fibrosis are started on the new treatment regimens, with other patients treated with existing pre-DAA regimens. Treating this smaller group of patients is estimated to result in an increase in initial drug expenditures of $7 billion in the first year for the population of California, one-third of the extra amount needed to treat all infected patients. Costs saved by reducing liver-related complications in this subgroup would total only 17% of added drug costs at five years, but at 20 years, estimated cost offsets would produce a net savings to the statewide health care system of approximately $1 billion.

We must emphasize several important limitations of our budget impact analyses. First, while there were sufficient data to perform a network meta-analysis for patients with genotype 1 infection, estimates could not be generated for all stratifications of interest for the model, and we could not even attempt quantitative synthesis for patients with genotypes 2 or 3. We therefore often had to resort to basing the input to the model on point estimates from individual studies, which in some cases involved small numbers of patients. Our results are therefore quite sensitive to the estimates of drug effectiveness and should be viewed with caution.

In addition, as described previously, we modeled only the immediate clinical effects of treatment as well as the potential downstream benefits of preventing liver-related complications. While we presented pooled rates of discontinuation due to adverse events from available clinical trial data, we assumed equally across all drug regimens that all patients completed their course of therapy and were fully compliant while doing so. This assumption likely does not adequately reflect the benefits of better adherence to newer regimens with shortened courses of interferon or no interferon at all.

For the 20-year time horizon analyses of clinical and economic outcomes, we did not try to include estimates of the impact of competing risks of morbidity and mortality for patients as they neared 80 years of age. If we had attempted to model these competing risks, the estimates of liver-related complications and resulting potential cost offsets would have been lower, serving to make the budget impact of newer regimens even more unfavorable.

We estimated the costs of medication using published wholesale acquisition costs or average wholesale prices.[7] Of note, however, telaprevir costs have increased substantially over the past 1.5 years, even as its use has declined to near zero.[6] We chose to model telaprevir costs using estimates from the time period in which it was considered the previous standard of care for triple therapy ($4,920 per week) rather than using a more current, and what we believe to be artificially-inflated, price.

Finally, our analyses did not consider other possible benefits to patients from greater treatment success, such as improved quality of life and reduced absenteeism from work or school. Full analysis of all potential outcomes and costs of these new treatment options will only be possible through additional data collection and/or the development of complex simulation models that approximate the natural history of hepatitis C and its treatment.

CTAF Public Meeting – Voting Results and Policy Issues

During a March 10, 2014 public meeting, the CTAF Panel deliberated and voted on key questions related to the comparative clinical effectiveness and comparative value of new treatments for hepatitis C. The key questions addressed the most important issues in applying the evidence to support clinical practice and medical policy decisions. Following its deliberation on the evidence and subsequent voting, the CTAF Panel engaged in a moderated discussion with a Policy Roundtable composed of clinical experts in liver disease, a patient advocate, payer representatives, and a representative from a manufacturer of one of the new drugs, all of whom were asked at the

meeting to disclose any conflicts of interest. This discussion was distilled into nine specific recommendations. The key themes are summarized below:

1. Even though the CTAF panel voted that the new drugs are likely superior in terms of clinical effectiveness for most patients and offer clinical benefits beyond current treatments, serious limitations in the evidence base remain. Further evidence is needed to more fully evaluate the comparative clinical effectiveness and value of these new treatments.
2. A majority of the CTAF Panel rated the new treatments as "low value" compared with older drugs due to the magnitude of the potential impact on health care budgets of treating large numbers of patients with these high-priced drug regimens. Because the financial impact of using these new drugs to treat all eligible patients with hepatitis C is untenable, policy makers should seek avenues to achieve reductions in the effective price of these medications.
3. Panel members and outside experts nearly all agreed that for both clinical and cost reasons, not every patient with hepatitis C needs to be immediately treated with the new drugs. Patients and providers should discuss the timing of treatment. Given the circumstances, it is reasonable to consider prioritizing treatment with the new drugs for patients who need urgent treatment and have advanced fibrosis or cirrhosis.
4. Additional policy measures to increase the likelihood of clinical benefit from treatment while reducing the financial impact should be considered. Payers seeking to achieve these goals should consider use of prior authorization criteria that a) require patient commitment, b) utilize "futility rules" that define when a lack of early response should lead to discontinuation of treatment, and c) require that the new drugs be prescribed by specialists with experience treating patients with hepatitis C.

Action Steps for Payers and Policymakers

The following action steps are designed to help payers and policymakers develop policies that encourage the appropriate use of new treatments for patients with hepatitis C.

1. **Given the limited number of experienced treating clinicians, the balance of risks and benefits for immediate treatment of patients without significant liver damage, and the financial impact of current high prices, it is reasonable to consider prioritizing coverage for treatment by the level of liver fibrosis.**

   Treating all eligible patients with hepatitis C with the new drug regimens is not clinically required nor is it feasible given constraints on clinical infrastructure and financial resources. Under these circumstances, it is reasonable to consider prioritizing coverage for the new drugs for patients who have advanced fibrosis or cirrhosis. The use of the drugs in patients with decompensated cirrhosis is not yet well studied and should be done only under the guidance of experts. While noting that symptoms of liver dysfunction alone are an unreliable means of assessing hepatic fibrosis, the clinical experts on a CTAF Policy Roundtable[1] indicated that patients with advanced fibrosis and cirrhosis (METAVIR scores of F3-F4), those who have liver cancer and are awaiting transplant, and those who are post-liver transplant have the greatest chance of benefiting from immediate treatment. Ideally, it would be desirable to cover the new treatments for all patients with hepatitis C to prevent progressive fibrosis. However, the clinical trial data are still new, and outcomes in the "real-world" are not yet available. Immediate treatment is not necessary in most cases, and allowing drugs to be further studied may be a better strategy for those patients who have little or mild fibrosis. If cost necessitates that not all patients be treated immediately, then using the level of liver fibrosis as a basis for patient selection offers the greatest likelihood of long-term clinical benefits while moderating the short-term financial impact on the health care system.

2. **Consider policy measures to increase the likelihood of clinical benefit from treatment while reducing the financial impact. Payers seeking to achieve these goals should consider developing prior authorization criteria that a) require patient commitment to and compliance with the treatment regimen, b) utilize "futility rules" that define when a lack of early response should lead to discontinuation of treatment, and c) require that**

[1] The Policy Roundtable at the March 10, 2014 CTAF meeting was composed of clinical experts in liver disease, a patient advocate, payer representatives, and a representative from a manufacturer of one of the new drugs, all of whom were asked at the meeting to disclose any conflicts of interest.

prescriptions of simeprevir and sofosbuvir be written by specialist physicians with experience treating patients with hepatitis C.[2]

a) Because the new drugs to treat hepatitis C have fewer side effects, greater patient compliance is expected. However, given the high cost of initial treatment, the risk that poor adherence would lead to the development of resistant viral strains, and the additional cost if a patient stops treatment and then starts again with a new treatment course, consider making coverage contingent upon a documented patient commitment to the planned course of treatment, including anticipated blood tests and office visits during and after treatment.

b) Given that good adherence to the new drugs is extremely likely to result in dramatic reductions in viral load within the first four weeks of treatment if the treatment is going to be effective, another prior authorization option would be to develop "futility rules" that require viral load monitoring and that would lead to cessation of coverage for further pills should the results show inadequate response.

c) Consider limiting prescribing of the new drugs to experienced hepatitis C experts. These clinicians have the knowledge to engage in discussions with patients about initiating treatment, they know well the side effects and adherence issues that are critical components of successful treatment, and they know how to monitor and care for patients who are on regimens combined with interferon and ribavirin. Over time, and with the introduction of more all-oral drug regimens, the care of patients with hepatitis C may be shared increasingly with primary care clinicians, but for the short-term it may be wise to consider limiting prescription of the newest drugs to experienced physicians and specialists.

"Fail-first" policies that require patients to try the first generation anti-viral treatments or interferon and ribavirin alone before receiving coverage for simeprevir or sofosbuvir do not appear to have support within the clinical community. This is because the side effect profiles and relative effectiveness of previous treatment options are viewed as inferior to the newer drugs.

Several payers have made their coverage policies for simeprevir and sofosbuvir public. These are currently being rapidly updated. Among those available are the following:

Simeprevir

- **Health Net:** https://www.healthnet.com/static/general/unprotected/html/national/pa_guidelines/olysio_natl.html

[2] See the Appendix for sample language from various prior authorization criteria for simeprevir and sofosbuvir.

- **Aetna:**
  http://www.aetna.com/products/rxnonmedicare/data/2014/GI/hepatitis_c.html
- **Anthem/Express Scripts:**
  http://www.anthem.com/provider/noapplication/f0/s0/t0/pw_e210962.pdf?na=pharminfo
- **CVS-Caremark:**
  http://www.caremark.com/portal/asset/FEP_Criteria_Olysio.pdf
- **Humana:**
  http://apps.humana.com/tad/tad_new/Search.aspx?criteria=simeprevir&searchtype=freetext&policyType=both
- **UnitedHealthcare:**
  https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Ox_MPUB_Future_Pharmacy/Notification_Olysio_514.pdf

Sofosbuvir

- **Health Net:**
  https://www.healthnet.com/static/general/unprotected/html/national/pa_guidelines/sovaldi_natl.html
- **Aetna:**
  http://www.aetna.com/products/rxnonmedicare/data/2014/GI/hepatitis_c.html
- **Anthem/Express Scripts:**
  http://www.anthem.com/provider/noapplication/f0/s0/t0/pw_e210963.pdf?na=pharminfo
- **CVS-Caremark:**
  http://www.caremark.com/portal/asset/FEP_Criteria_Sovaldi.pdf
- **Humana:**
  http://apps.humana.com/tad/tad_new/Search.aspx?criteria=sofosbuvir&searchtype=freetext&policyType=both
- **UnitedHealthcare:**
  https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Ox_MPUB_Future_Pharmacy/Notification_Sovaldi_514.pdf

3. Consider covering on a limited basis the off-label use of simeprevir and sofosbuvir together to treat patients who need immediate treatment and are interferon-ineligible.

A slight majority of the CTAF Panel (8 members) voted that the evidence was adequate to demonstrate that the combination of simeprevir and sofosbuvir was more effective than no treatment at all for genotype 1 patients who were interferon-ineligible, but only six members of the

CTAF Panel voted that the evidence was adequate to show that the off-label combination was better than 24 weeks of sofosbuvir plus ribavirin. Even when compared with no treatment, the CTAF Panel rated sofosbuvir plus simeprevir as "low value" on the basis of its potential budget impact. During the discussion, however, the clinical experts on the Policy Roundtable indicated that for certain select patients who are truly ineligible for interferon and who are also felt to require immediate treatment, it may make sense to consider using sofosbuvir plus simeprevir since it can be used for only 12 weeks instead of 24 for sofosbuvir alone, and it is thus likely to be more effective and less expensive.

4. Closely monitor evolving evidence and clinical guidelines to ensure that prior authorization criteria and other coverage policies remain up-to-date with the most recent evidence.

The evidence on the comparative effectiveness and value of new treatment options for hepatitis C will continue to evolve rapidly over the next several years. Payers and policymakers must ensure that systems are in place to keep all coverage policies up to date with new evidence. Many organizations in the United States and internationally will be performing periodic evidence reviews on these drugs, and payers and policymakers can gain important insights into the strength of evidence by comparing the findings of these reviews. Similarly, payers should seek to use only high-quality evidence-based clinical guidelines as input into coverage determinations. All guidelines for the treatment of hepatitis C that are considered as part of coverage determinations should be developed using best practices, including ratings of the strength of evidence, clarity about the role of various organizations involved in developing the guidelines, and complete openness about potential conflicts of interest of individual guideline committee members. The Institute of Medicine (IOM), an independent organization of scientists that analyzes available data and provides advice on medical issues, recommends that chairs of guideline committees should have no conflicts of interest if possible, and that the entire group developing the guidelines should also be free of ties to industry; if that is not possible, then at least half of the members should meet this criterion.

Organizations that have produced clinical guidelines on hepatitis C treatment and may produce updated ones in the future include:

- US Department of Veterans Affairs (VA): http://www.hepatitis.va.gov/provider/guidelines/2014hcv/index.asp
- American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA)/International Antiviral Society – USA (IAS USA): http://www.hcvguidelines.org
- National Institute for Health and Care Excellence (NICE): http://cks.nice.org.uk/hepatitis-c

- European Association for the Study of the Liver (EASL): http://www.easl.eu/2013HCVguideline
- Canadian Association for the Study of the Liver (CASL): http://www.hepatology.ca
- The Japan Society of Hepatology (JSH): http://JSH2014HCVguidelines

5. **Because the financial impact of using these new drugs to treat all eligible patients with hepatitis C is untenable, payers and policymakers should consider innovative contracting mechanisms and other avenues to achieve reductions in the effective price of the new drugs to treat hepatitis C.**

Very large numbers of patients could potentially benefit from receiving the new drugs for hepatitis C. However, the prices of the new drugs, highlighted by sofosbuvir's price of $1,000/pill and $84,000 per 12 weeks of treatment, when multiplied by the number of eligible patients, create a financial burden that was considered by the CTAF Panel and several of the Policy Roundtable participants to be untenable. Competition and market pressure may result in lower prices when additional treatment options become available within the next 1-2 years. For now, however, actions that payers and policymakers can consider include innovative contracting approaches in which differential prices are paid for the treatment of patients with different genotypes, based on the strength of the underlying evidence; risk-sharing contracts in which manufacturers rebate the price paid for patients who do not achieve the desired clinical outcome; and reference pricing that involves setting the price for a new treatment at the lowest "reference" price paid for any existing treatment with equivalent effectiveness. For example, payers may wish to examine closely the evidence in the CTAF report on the comparative effectiveness of simeprevir and sofosbuvir for treatment-experienced patients with genotype 1: the CTAF Panel voted that the evidence cannot distinguish between the effectiveness of the two drugs in this important patient subpopulation.

6. **Recognize the variation in quality of existing clinical guideline development processes, and partner with patients and clinicians to advocate for guidelines that reflect high-quality evidence and are developed by committees free of serious conflicts of interest.**

Because treatment guidelines serve an important role in informing patients and clinicians, the guidelines should be developed using best practices, including ratings of the strength of evidence, transparency regarding the role of various organizations involved in guideline development, and full transparency regarding potential conflicts of interest of individual guideline committee members, with limits on the proportion of committee members who receive direct or indirect financial support from manufacturers. This will allow patients, providers, and other stakeholders to fully believe in the objectiveness and trustworthiness of key clinical guidelines.

The clinical guidelines for the treatment of hepatitis C developed by the American Association for the Study of Liver Diseases (AASLD), the Infectious Disease Society of America (IDSA), and the International Anti-Viral Society-USA do not yet address issues about prioritizing which patients should be treated first, nor do they include consideration of the costs of different treatment options. An April 17, 2014 article in the *New York Times* noted that several specialty societies are beginning to use cost data to rate the value of treatments in their joint clinical practice guidelines and performance standards.

The Institute of Medicine (IOM), an independent organization of scientists that analyzes available data and provides advice on medical issues, recommends that chairs of guideline committees should have no conflicts of interest if possible, and that the entire panel should also be free of ties to industry; if that is not possible, then at least half of the members should meet this criterion. The International Committee of Medical Journals Editors, a group of journal editors who suggest policies for how studies should be reported, edited, and published, advise that guidelines panelists be free of ties to industry for at least 36 months to ensure any unintentional biases do not influence their decisions. According to their website, well over half of the individual committee members developing the AASLD/IDSA guidelines, including the committee chairmen, had either direct (e.g., consulting) and/or indirect support (for research) from the manufacturers of the new hepatitis C drugs.

More information on the IOM recommendations may be found at this link:

- Institute of Medicine: http://www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx

7. Consider engaging with manufacturers, clinicians, and patients to implement policies that support evidence generation to guide future decision making.

As noted above, the CTAF Panel discussed the limited evidence available (single arm, open-label, non-randomized studies with small numbers of patients) to assess the comparative clinical effectiveness of the new treatments for hepatitis C. The CTAF Panel stated that more robust studies are needed moving forward, both for the current FDA-approved drugs and for subsequent additions to the range of therapeutic options. During the discussion, it was suggested that manufacturers consider engaging with payers and independent review organizations to discuss evidence standards at the same time they are generating evidence for review by the FDA. It was also recommended that payers implement policies to support evidence generation – e.g., provide coverage only if patients are enrolled in a practical clinical trial or an observational registry. The relative paucity of evidence for genotype 1, treatment-experienced patients and for genotype 3 patients in particular were noted as the most significant needs for further evidence at this time.

8. Support efforts to build capacity among clinicians to treat patients with hepatitis C.

To increase the number of physicians available to treat patients who have hepatitis C, additional investments should be made in training programs for primary care physicians. Emerging all-oral hepatitis C treatments may have low side effect profiles and very broad applicability across patients with different genotypes and history of prior treatment, opening up the possibility that primary care physicians can safely prescribe hepatitis C treatments and help improve access to care for many patients.

Efforts are underway by the Department of Health and Human Services (HHS) and Centers for Disease Control and Prevention (CDC) to increase education and training in hepatitis C among non-specialist physicians and providers. Using the Project ECHO (Extension for Community Healthcare Outcomes) model, specialist training of primary care providers directly and remotely has been shown to be extremely desired among primary care physicians and extremely effective in terms of patient outcomes. By investing in these types of training programs, a smooth transition in the delivery of patient care can be achieved as hepatitis C becomes a disease that is treated by a wider variety of physicians.

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APPENDIX

Comparative Prior Authorization Approval Criteria: Simeprevir

Color coding:

Health Net | Anthem/Express Scripts | Aetna | CVS/Caremark | Humana | Clinical Expert

Patient criteria

1. The patient must be at least 18 years of age.
2. The patient must have a diagnosis of chronic hepatitis C with compensated liver disease.*
3. The patient must have documented genotype 1 HCV infection.
4. Patients with genotype 1a must be screened for the presence of virus with the NS3 Q80K polymorphism.
5. A planned course of treatment is documented in medical record.
6. The patient verbally or in writing commits to the documented planned course of treatment including anticipated blood tests and visits, during and after treatment.
7. Neither the patient nor the partner of the patient is pregnant.
8. If patient or their partner are of child bearing age, the patient has been or will be instructed to practice effective contraception during therapy and for 6 months after stopping ribavirin therapy.

Olysio (simeprevir) therapy is not considered medically necessary for patients with the following concomitant conditions:

- Patient has genotype 1a infection with Q80K polymorphism.
- Patient has previously received therapy with a treatment regimen that included a HCV NS3/4A protease inhibitor.
- Concurrent use with other HCV NS3/4A protease inhibitors or sofosbuvir.
- Coadministration with any one of the following medications that are either potent CYP3A4/5 inducers or CYP3A4/5 inhibitors:
  - Alpha 1-Adenoreceptor Antagonist: alfuzosin
  - Antimycobacterial: rifampin
  - Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine
  - GI Motility Agent: cisapride
  - Herbal Products: St. John's Wort
  - HMG-CoA Reductase Inhibitors: atorvastatin, lovastatin, simvastatin
  - Neuroleptic: pimozide
  - PDE 5 Enzyme Inhibitors: Revatio (sildenafil) or Adcirca (tadalafil) when used for the treatment of pulmonary arterial hypertension
  - Sedative/hypnotics: triazolam, orally administered midazolam

Health Net Anthem/Express Scripts Aetna CVS/Caremark Humana Clinical Expert

***Compensated Liver Disease:**

Compensated liver disease (i.e., stable liver problems; a diseased liver that is functional)

According to the American Association for the Study of Liver Diseases (AASLD, 2009), the specific criteria for compensated liver disease include ALL of the following: a total serum bilirubin < 2 g/dL; INR < 1.7; albumin > 3.5 g/dL; and no evidence of hepatic encephalopathy or ascites. However, these criteria do not establish a comprehensive definition of compensated liver disease. In fact, the AASLD guidelines refer to compensated liver disease as Grade A based on the Child Pugh-Turcotte classification scoring system, shown below:

Parameters			
Points assigned	**1 point**	**2 points**	**3 points**
Encephalopathy	None	Minimal	Advanced coma
Ascites	None	Easily controlled	Poorly controlled
Serum bilirubin	<2mg/dL	2-3 mg/dL	>3 mg/dL
Serum albumin	>3.5 g/dL	2.8-3.5 g/dL	<2.8 g/dL
INR	INR <1.7	INR 1.7-2.3	INR >2.3

Child Pugh-Turcotte Score Interpretation
Class A 5-6 points Well compensated liver disease
Class B 7-9 points Significant functional compromise
Class C 10-15 points Uncompensated liver disease

The prescribing physician must provide clinical evidence to establish a patient's cirrhosis status – as cirrhosis or no-cirrhosis. Supportive findings of cirrhosis if any 1 of the following:

1. Liver biopsy stage F3 or F4 or significant fragmentation
2. Radiological imaging with findings suggestive of cirrhosis
3. Platelet count <140,000
4. Physical findings consistent with cirrhosis
5. Evidence of portal hypertension
6. Fibroscan evaluation with F3 or F4 result.
7. Fibrosure measurement with F3 or F4 result.
8. APRI score
9. Or other documented finding consistent with cirrhosis

Clinician criteria
Patient is being supervised by a physician with experience in the treatment of hepatitis C infection.

Health Net | Anthem/Express Scripts | Aetna | CVS/Caremark | Humana | Clinical Expert

Drug regimen criteria

Olysio must be used in combination with peginterferon alfa and ribavirin (triple therapy).

Approval duration

Option 1: 12 weeks (No interim assessment required)

Option 2: Discontinuation of Dosing: Response Guided Treatment (RGT)

HCV RNA viral load by quantitative assay at Treatment Week (TW) 4, TW12 and TW24 are required to determine length of approval.

Treatment-Naive and Prior Relapse Patients:

Initial authorization is 8 weeks.

1. If HCV RNA levels are less than 25 IU/mL at week 4, authorize Olysio for an additional 4 weeks AND authorize peginterferon alfa and ribavirin dual therapy for an additional 8 weeks. Olysio triple therapy complete at week 12. Recheck viral load at week 12 to evaluate peginterferon alfa and ribavirin continuation.
2. If HCV RNA levels are greater than or equal to 25 IU/mL at week 4, no additional authorization of Olysio triple therapy.
3. If HCV RNA levels are less than 25 IU/mL at week 12, authorize peginterferon alfa and ribavirin for an additional 8 weeks. Peginterferon alfa and ribavirin dual therapy complete at week 24.
4. If HCV RNA levels are greater than or equal to 25 IU/mL at week 12, no additional authorization of peginterferon alfa and ribavirin.

Prior Partial and Null Responder Patients:

Initial authorization is 8 weeks.

1. If HCV RNA levels are less than 25 IU/mL at week 4, authorize Olysio for an additional 4 weeks AND authorize peginterferon alfa and ribavirin dual therapy for an additional 8 weeks. Olysio triple therapy complete at week 12. Recheck viral load at week 12 to evaluate peginterferon alfa and ribavirin continuation.
2. If HCV RNA levels are greater than or equal to 25 IU/mL at week 4, no additional authorization of Olysio triple therapy.
3. If HCV RNA levels are less than 25 IU/mL at week 12, authorize peginterferon alfa and ribavirin dual therapy for an additional 12 weeks. Recheck viral load at week 24 to evaluate peginterferon alfa and ribavirin continuation.
4. If HCV RNA levels are greater than or equal to 25 IU/mL at week 12, no additional authorization of peginterferon alfa and ribavirin.
5. If HCV RNA levels are less than 25 IU/mL at week 24, authorize peginterferon alfa and ribavirin for an additional 20 weeks. Peginterferon alfa and ribavirin dual therapy complete at week 48.
6. If HCV RNA levels are greater than or equal 25 IU/mL at week 24, no additional authorization of peginterferon alfa and ribavirin.

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Treatment Stopping Rules in Any Patient with Inadequate On-Treatment Virologic Response
Olysio (simeprevir) will be approved for 12 weeks.

HCV RNA	Action
Treatment Week 4: greater than or equal to 25 IU/mL	Discontinue Olysio, peginterferon alfa and ribavirin
Treatment Week 12: greater than or equal to 25 IU/mL	Discontinue peginterferon alfa and ribavirin (treatment with Olysio is complete at Week 12)
Treatment Week 24: greater than or equal to 25 IU/mL	Discontinue peginterferon alfa and ribavirin

Treatment regimens recommended by AASLD that are not included in current prior authorization criteria

Recommended regimen for treatment-naive patients with HCV genotype 1 who are not eligible to receive IFN.
Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg) for 12 weeks is recommended for IFN-ineligible patients with HCV genotype 1 infection, regardless of subtype.

Recommended regimen for HCV genotype 1 PEG/RBV (without an HCV protease inhibitor) nonresponder patients:
Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for retreatment of HCV genotype 1 infection, regardless of subtype or IFN eligibility

Comparative Prior Authorization Approval Criteria: Sofosbuvir

Color coding:
Health Net Anthem/Express Scripts Aetna CVS/Caremark Humana Clinical Expert

Patient criteria

1. The patient must be at least 18 years of age.
2. The patient must have a diagnosis of chronic hepatitis C with compensated liver disease.*
3. Liver biopsy showing fibrosis corresponding to a Metavir score of greater than or equal to 2 or Ishak score of greater than or equal to 3 or other accepted test demonstrating liver fibrosis.
4. Absence of renal impairment: eGFR must be > 30mL/min/1.73m^2
5. Absence of end stage renal disease (ESRD).
6. A planned course of treatment is documented in medical record.
7. The patient verbally or in writing commits to the documented planned course of treatment including anticipated blood tests and visits, during and after treatment.
8. Neither the patient nor the partner of the patient is pregnant.
9. If patient or their partner are of child bearing age, the patient has been or will be instructed to practice effective contraception during therapy and for 6 months after stopping ribavirin therapy.
10. Genotype 1: Member must have failed to achieve SVR on a prior regimen containing a HCV NS3/4A protease inhibitor.

***Compensated Liver Disease:**

Compensated liver disease (i.e., stable liver problems; a diseased liver that is functional)

According to the American Association for the Study of Liver Diseases (AASLD, 2009), the specific criteria for compensated liver disease include ALL of the following: a total serum bilirubin < 2 g/dL; INR < 1.7; albumin > 3.5 g/dL; and no evidence of hepatic encephalopathy or ascites. However, these criteria do not establish a comprehensive definition of compensated liver disease. In fact, the AASLD guidelines refer to compensated liver disease as Grade A based on the Child Pugh-Turcotte classification scoring system, shown below:

Parameters			
Points assigned	**1 point**	**2 points**	**3 points**
Encephalopathy	None	Minimal	Advanced coma
Ascites	None	Easily controlled	Poorly controlled
Serum bilirubin	<2mg/dL	2-3 mg/dL	>3 mg/dL
Serum albumin	>3.5 g/dL	2.8-3.5 g/dL	<2.8 g/dL
INR	INR <1.7	INR 1.7-2.3	INR >2.3

Child Pugh-Turcotte Score Interpretation

Class A	5-6 points	Well compensated liver disease
Class B	7-9 points	Significant functional compromise
Class C	10-15 points	Uncompensated liver disease

Health Net Anthem/Express Scripts Aetna CVS/Caremark Humana Clinical Expert

The prescribing physician must provide clinical evidence to establish a patient's cirrhosis status – as cirrhosis or no-cirrhosis. Supportive findings of cirrhosis if any 1 of the following:

1. Liver biopsy stage F3 or F4 or significant fragmentation
2. Radiological imaging with findings suggestive of cirrhosis
3. Platelet count <140,000
4. Physical findings consistent with cirrhosis
5. Evidence of portal hypertension
6. Fibroscan evaluation with F3 or F4 result
7. Fibrosure measurement with F3 or F4 result
8. APRI score
9. Or other documented finding consistent with cirrhosis

Clinician criteria
Patient is being supervised by a physician with experience in the treatment of hepatitis C infection.

Drug Regimen Criteria
Requests for concomitant use of two or more of the following; Incivek (telaprevir), Victrelis (boceprevir), Olysio (simeprevir), or Sovaldi (sofosbuvir) will not be approved.

AASLD treatment regimens not included in current prior authorization criteria

Recommended regimen for treatment-naive patients with HCV genotype 1 who are not eligible to receive IFN.
Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg) for 12 weeks is recommended for IFN-ineligible patients with HCV genotype 1 infection, regardless of subtype.

Recommended regimen for HCV genotype 1 PEG/RBV (without an HCV protease inhibitor) nonresponder patients:
Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for retreatment of HCV genotype 1 infection, regardless of subtype or IFN eligibility

Different definitions of "interferon ineligible/intolerant":

Health Net
Interferon ineligible (patients in whom interferon therapy is contraindicated due to such conditions as anemia, alcohol abuse, advanced or decompensated cirrhosis, or severe psychiatric disorder) or interferon-intolerant (patients who discontinued interferon therapy prematurely due to side effects)

Aetna
Recent suicidal attempts, severe depression, previous serious adverse events

Anthem/Express Scripts
1. Autoimmune hepatitis; **OR**
2. Child Pugh-Turcotte score greater than 6 (Class B or C) before or during interferon treatment; **OR**
3. Known hypersensitivity to interferon products

Humana
An interferon ineligible member [is] defined as one of the following:
1. Contraindication to interferon therapy defined as:
    a. known hypersensitivity to interferon alfa
    b. autoimmune hepatitis
    c. hepatic decompensation
    d. pregnant females or male partners of pregnant females
    e. hemoglobinopathies
    f. creatinine clearance less than 50 mL/min
    g. coadministration with didanosine; OR
2. Previous intolerance to an interferon alfa containing regimen resulting in discontinuation of therapy

CVS/Caremark
Interferon ineligible, intolerant, or unwilling

Clinical Expert
Interferon ineligible or intolerant, supported by any of the following:
1. platelet count <80,000/mm^3
2. decompensated liver cirrhosis (Child Pugh-Turcotte class B or C qualifying events)
3. severe mental health conditions (which may be exacerbated by interferon)
4. autoimmune diseases that may be exacerbated by interferon-mediated immune modulation
5. inability to complete a prior treatment course due to adverse effects experienced while on treatment which were related to interferon
6. poorly controlled diabetes mellitus, thyroid condition
7. leukopenia or neutropenia
8. significant medical risk if were to have a drop in intake due to anorexia, nausea, weight loss