Drug Use Research & Management Program
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Abbreviated Class Update: Hepatitis C

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

Last Review: July 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:
- A new section from the poor quality AASLD/IDSA guidelines on when and in whom to initiate HCV therapy recommends treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir F3), those with compensated cirrhosis (Metavir F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C.[1]
- There remains insufficient evidence on the long-term efficacy and safety of sofosbuvir based treatment in interferon ineligible genotype 1 (GT1) patients. New guidance from NICE does not recommend sofosbuvir in this patient population.[2]
- There is low quality evidence that the vast majority of subjects treated with sofosbuvir reach an HCV RNA level below the limit of quantification (<25 IU/ml) at or before week 4 of therapy. Monitoring for response at week 4 of therapy is recommended to evaluate for adherence and efficacy.

Recommendations
- Recommend including additional changes to PA criteria (Appendix 1):
  - Excluding patients who have had previous treatment with an oral direct acting antiviral
  - Requiring a HCV RNA level at week 4 to determine response. If the HCV RNA is detectable at week 4 or at any time point thereafter, reassess HCV RNA in 2 weeks. If the HCV RNA increases or if the 8 week HCV RNA is detectable, discontinue treatment.

- Consider excluding GT1 interferon ineligible patients due to insufficient evidence in this population.
- With evolving pipeline of medications for the treatment of hepatitis C, create general Hepatitis C prior authorization criteria to ensure new treatments are being used appropriately until they can be reviewed in full by the Pharmacy & Therapeutics Committee (Appendix 2).
- The sale and distribution of telaprevir has been discontinued; remove from PDL.

Previous Conclusions and Recommendations:

- 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.[3,4]
- 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.[5]
- 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.[6,7]
- 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.[8]
- 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.[9,10]
- 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.[11]
- 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.[11]
- 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.[12] 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. [12] 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.[13] 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.[8]

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. [12] Previous standard of care for Genotype 1 CHC is a protease inhibitor (boceprevir or telaprevir) plus pegylated interferon and ribavirin.[14] This is based on several RCTs showing improved rates of SVR (63-79%) with triple therapy compared to 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 previous 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.[15]

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-relate 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.[16]

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.[17] 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.

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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.[13] 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. Since approval and uptake of these newer agents, Vertex has discontinued the sale and distribution telaprevir (Incivek®).[18]

Methods:
A Medline literature search beginning July 2014 (since the most recent Hepatitis C Class Update) and ending August 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:
None

Clinical Guidelines:

American Association for the Study of Liver Diseases (AASLD)/ Infectious Diseases Society of America (IDSA)
Guidelines on when and in whom to initiate HCV therapy were released by the AASLD and IDSA.[1] This is one section of the entire guideline, which was previously discussed.[19] However, the guidelines have many limitations and the overall methodological quality of the guidance was poor.[8] The panel lacked non-specialist members and there was no assessment of risk of bias for individual studies. The authors and sponsors of the guidance had multiple conflicts of interest. The following additional recommendations were provided in this section:

- The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of SVR (Class 1 level of evidence, Level A recommendation).
- Treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir F3), those with compensated cirrhosis (Metavir F4) (Class 1, Level A), liver transplant recipients (Class 1, Level B), and patients with severe extrahepatic hepatitis C (Class 1, Level B).
- Based on available resources, treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority. This includes patients with:
    - Fibrosis (Metavir F2) (Class 1, Level B).
    - HIV-1 coinfection (Class 1, Level B)
    - HBV coinfection (Class IIa, level C)
    - Other coexistent liver disease (Class IIa, Level C)
    - Debilitating fatigue (Class 11a, Level B)

    - Type 2 Diabetes mellitus (insulin resistant) (Class IIa, Level B)
    - Porphyria cutanea tarda (Class IIb, Level C)
- Persons whose risk of transmission is high should be prioritized for treatment (Class IIa, Level C):
    - Men who have sex with men (MSM) with high-risk sexual practices
    - Active injection drug users
    - Incarcerated persons
    - Persons on long-term hemodialysis
- An assessment of the degree of hepatic fibrosis, using noninvasive testing of liver biopsy, is recommended (Class 1, level A)
- Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred (Class 1, Level C)

Canadian Agency for Drugs and Technologies in Health (CADTH):

In August 2014, CADTH released draft recommendations for direct acting antiviral agents for chronic Hepatitis C Genotype 1.[20] Evidence informed recommendations were developed by the Canadian Drug Expert Committee. The summary of recommendations are as followed:

- Recommends simeprevir daily for 12 weeks, in combination with peginterferon and ribavirin for 24 to 48 weeks as the protease inhibitor of choice for treatment-naïve patients or for treatment-experienced patients with prior relapse.
    - This is based on evidence showing that simeprevir was more effective in achieving SVR compared with dual therapy and showed no statistically significant difference compared with other protease inhibitors based on indirect evidence.
    - For partial and null responders to dual therapy with peginterferon and ribavirin, there is insufficient evidence to identify an optimal therapy and the committee was unable to make a recommendation at this time.
- No definitive recommendation regarding the place in therapy for sofosbuvir, relative to available protease inhibitors, can be made at this time.
- Recommends that treatment should be offered only to persons living with chronic hepatitis C who have fibrosis stages F2, F3, or F4.
    - In all analyses, treatment of patients with higher grades of fibrosis was more cost-effective.
- Persons in whom a direct acting antiviral plus peginterferon and ribavirin regimen has failed should not be retreated with another direct acting antiviral plus peginterferon ribavirin regimen.
    - There is insufficient evidence to evaluate efficacy of retreatment.

The National Institute for Health and Care Excellence (NICE):

NICE recently released an appraisal document for sofosbuvir in the treatment of chronic hepatitis C.[2] This is still not the final appraisal and will go through further public comment processes. The following preliminary recommendations are given:

- Sofosbuvir, in combination with peginterferon alfa and ribavirin, is recommended as an option for treatment GT1 CHC in adults.
- Sofosbuvir, in combination with peginterferon and ribavirin, is recommended as an option for treatment genotype 3 CHC in adults with cirrhosis.
- Sofosbuvir, in combination with peginterferon alfa and ribavirin, is recommended as an option for treatment genotype 3 CHC in adults without cirrhosis, only if they had treatment for hepatitis C before.
- Sofosbuvir, in combination with peginterferon alfa and ribavirin, is not recommended for treatment genotype 4, 5, and 6 chronic hepatitis C in adults.
- Sofosbuvir, in combination with ribavirin alone is not recommended for treating adults with genotype 1, 4, 5 and 6 CHC.
- Sofosbuvir, in combination with ribavirin, is recommended as an option for treating genotype 2 CHC in adults only if they:
    - Have not had treatment for chronic hepatitis C before and are intolerant to or ineligible for interferon therapy or

- Have had treatment for chronic hepatitis C before, regardless of interferon eligibility.
- Sofosbuvir, in combination with ribavirin, is recommended as an option for treating genotype 3 CHC only in adults with cirrhosis.

Monitoring:

In April 2014, the European Association for the Study of the Liver (EASL) published guidelines for the treatment of HCV, including recommendations for monitoring.[3]

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

Department of Veterans Affairs (VA)

The VA National Hepatitis C Resource Center Program released treatment considerations for Chronic HCV earlier in 2014.[5] The panel provided 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 (i.e., >1 log10 IU/mL from nadir) or if the 8-week level remains detectable (HCV RNA is ≥25 IU/mL), discontinuation of all treatment should be strongly considered (Strong recommendation; expert opinion). In addition, the panel notes that to assess treatment response, commercial assays that have a lower limit of HCV RNA quantification (LLOQ) of ≤25 IU/mL is strongly recommended.

The following criteria were used in the NEUTRINO protocol to define on-treatment virologic failure[21] (note, HCV RNA levels were checked at least every 2 weeks using an assay with an LLOQ of <25 IU/mL), and provide more detailed information about specific situations where discontinuation of sofosbuvir-based therapy should be strongly considered4:

•HCV RNA is ≥LLOQ (confirmed on at least one repeat test) after having previously had HCV RNA<LLOQ while on treatment
•>1 log10 IU/ml increase in HCV RNA (confirmed on at least one repeat test) from nadir while on treatment
•HCV RNA persistently ≥LLOQ through 8 weeks of treatment

In the NEUTRINO study, by week 4, the proportion of patients with this reduced level of HCV RNA was 99%, a rate that was maintained throughout the treatment period. SVR12 rates were 90% (295/327).

UpToDate

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According to UpToDate, the vast majority of subjects treated with sofosbuvir reach an HCV RNA level below the limit of quantification (<25 IU/ml) at or before week 4 of therapy (97% in one study of HIV/HCV coinfected patients).[22] Any detectable HCV RNA should raise the possibility of nonadherence and patients being treated with a 24 course of sofosbuvir who have detectable HCV RNA at week 12 should have the HCV RNA repeated. A persistently detectable HCV RNA should trigger consideration of discontinuation.

Pipeline:

The pipeline is expected to expand quickly over the next few years. The interferon-free all oral combination of direct acting antivirals, daclatasvir and asunaprevir, is expected to be approved in September. It was recently approved for the treatment of patients with HCV GT1 in Japan.[23] Daclatasvir plus asunaprevir has been studied in a phase 3 multicohort study[24] and an open-label phase 3 study[25] in treatment naive patients with HCV genotype 1b. IT was also studied with or without peginterferon and ribavirin in null responders.[26] Daclatasvir has also been studied in combination with sofosbuvir in previously treated or untreated chronic HCV patients with genotype 1, 2, and 3 in a open-label study.[27]

The new direct acting antiviral ledipasvir is expected to be FDA approved by late 2014 and has been studied in combination with sofosbuvir in HCV GT 1 patients.[28–30]

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Appendix 1: Prior authorization Criteria

Sofosbuvir (Sovaldi®)

Goal(s) :

- Approve cost effective treatments of chronic hepatitis C which are supported by the medical literature when there is available evidence. When evidence is lacking, consult with local specialists and the community standard.

Length of Authorization

- Initial trial of 8 weeks
- Continuation of therapy up to 24 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 the request for treatment of Chronic Hepatitis C Virus?	**Yes:** Go to #3	**No:** Pass to RPh, Deny For Appropriateness
3. Is the request for continuation of therapy?	**Yes:** Go to "Continuation of Therapy"	**No:** Go to #4
4. Has the patient had previous treatment (full or incomplete course) with an oral direct acting antiviral that was FDA approved after 2012 (including sofosbuvir and simeprevir)?	**Yes:** Pass to RPh; Deny For Appropriateness	**No:** Go to #5
5. Is the medication being prescribed by or in consultation with a hepatologist or gastroenterologist with experience in Hepatitis C?	**Yes:** Go to #6	**No:** Pass to RPh, Deny For Appropriateness Forward to DMAP for further review to determine appropriateness of prescriber
6. Does the patient have a biopsy or other non-invasive technology (Fibroscan), including serum tests (Fibrosure, Fibrotest) to indicate severe fibrosis (stage 4) OR radiologic, laboratory, or clinical evidence of cirrhosis without ongoing progressive decompensation (MELD score between 8 and 11), and expected survival from non-HCV associated morbidity should be greater than 5 years?	**Yes:** Go to #11	**No:** Go to #7 **Note**: Patients with a MELD score >11 may be eligible for therapy, but only after review by the DMAP medical director. Forward fee-for-service cases to DMAP for Medical Director

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		Review and notify requesting provider of pending review.
7. Does the patient have one of the following extrahepatic manifestations of hepatitis C and who have formal documentation from a relevant specialist that their condition is HCV related, and expected survival from non-HCV associated morbidity should be greater than 5 years? a. Vasculitis b. Glomerulonephritis c. Cryoglobulinemia d. Lymphoma	**Yes:** Go to #11	**No:** Go to #8
8. Does the patient have a HIV coinfection with cirrhosis (Stage 4 disease), and expected survival from non-HCV associated morbidity should be greater than 5 years?	**Yes:** Go to #9	**No:** Go to #10
9. Is the patient under the supervision of an HIV specialist?	**Yes:** Go to #11	**No:** Pass to RPh; Deny (medical appropriateness)
10. Does the patient have Hepatitis C Virus in the transplant setting, including the following scenarios: a. Patient is listed for a transplant and it is essential to prevent recurrent hepatitis C infection post-transplant b. Post-transplant patients with Stage 4 fibrosis c. Post-transplant patients with fibrosing cholestatic hepatitis due to HCV infection **and** expected survival from non-HCV associated morbidity should be greater than 5 years?	**Yes:** Go to #11 **Note**: Patients in the transplant setting may be eligible for therapy, but only after review by the DMAP medical director. Forward fee-for-service cases to DMAP for Medical Director Review and notify requesting provider of pending review.	**No:** Pass to RPh: Deny (medical appropriateness) **Note:** Other Scenarios not included can be brought to the Medical Director on a case by case basis
11. If applicable, has the patient been abstinent from IV drug, illicit drugs and marijuana use, AND alcohol abuse for ≥ 6 months?	**Yes**: Go to #12	**No:** Pass to RPh, Deny for appropriateness
12. 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 #13
13. Does the patient have a baseline HCV RNA level?	**Yes:** Record value and go to #14 Note: Next HCV RNA level required at week 4 of treatment (see continuation criteria	**No:** Pass to RPh; request provider obtain baseline lab value
14. What Hepatitis C genotype is the patient? Record Genotype:	Record Genotype and go to #15	
15. Does the patient have genotype 1 or 4 chronic hepatitis C?	**Yes:** Go to # 16	**No:** Go to #19
16. 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 initial 8 weeks for 12 weeks of total therapy	**No:** Go to #17
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 initial 8 weeks for12 weeks total therapy	**No:** Pass To RPh; Deny for Appropriateness

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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 initial 8 weeks 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 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 • Severe cytopenias • Other comorbidities that would be exacerbated by interferon use Note: Patient's or prescribers not wanting to go through treatment with interferon does not meet the criteria for being "interferon ineligible"	**Yes:** Approve for 8 weeks initial fill for a total 24 weeks of therapy	**No:** Pass To RPh; Deny for Appropriateness

Continuation of Therapy- Sofosbuvir (Assess after 4 weeks of treatment)		
1. Has the patient been adherent to and tolerated initial therapy?	**Yes**: Go to #2	**No:** DENY (Medical Appropriateness)
2. Is the HCV RNA level at week 4 detectable (HCV RNA is ≥25 IU/mL),?	**Yes:** reassess HCV RNA in 2 weeks. Go to #3	**No:** Go to #4
3. Has the HCV RNA increased (i.e., >1 log10 IU/mL from nadir)?	**Yes:** Discontinue treatment	**No:** Recheck in 2 weeks (week 8 of treatment). Go to #4
4. Is the 8 week HCV RNA detectable (HCV RNA is ≥25 IU/mL),?	**Yes:** Discontinue treatment	**No:** Approve for additional 4-16 weeks based on genotype and regimen

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

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

*****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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Appendix 2: Hepatitis C PA Criteria

Hepatitis C

Goal(s):

- Approve cost effective treatments of chronic hepatitis C which are supported by the medical literature when there is available evidence. When evidence is lacking the approval criteria reflect a community standard developed in consultation with local specialists.
- Provide consistent patient evaluations across all hepatitis C treatments

Requires PA:

- All drug regimens in the Hepatitis C PDL Class

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the request for treatment of Chronic Hepatitis C?	**Yes:** Go to #3	**No:** Pass to RPh; Deny for appropriateness.
3. Is the request for continuation of therapy?	**Yes:** Go to specific regimen PA Criteria	**No:** Go to #4
4. What regimen is requested?	**Document and go to #5**	
5. Does the regimen contain a drug not yet reviewed by P&T?	**Yes:** Pass to RPh; Deny for appropriateness. Forward to DMAP for further review to determine appropriateness and coverage in light of most recent community standards and comorbidity.	**No:** Go to #6

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Approval Criteria		
6. Is the regimen being prescribed by or in consultation with a hepatologist or gastroenterologist with experience in hepatitis C?	**Yes:** Go to #7.	**No:** Pass to RPh; Deny for appropriateness. Forward to DMAP for further review to determine appropriateness of prescriber.
7. What genotype and stage does the patient have?	**Document and go to #8**	
8. Has the patient been abstinent from IV drugs, illicit drugs, marijuana use AND alcohol abuse for greater than or equal to 6 months?	**Yes**: Go to specific regimen PA Criteria.	**No**: Pass to RPh; Deny for medical appropriateness.

P&T / DUR Action:
Revision(s):
Initiated:

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