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Month/Year of Review: September 2013
PDL Classes: Antivirals – Hepatitis C agents

Date of Last Review: Drug January 2012
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Current Status of PDL Class:

- **Preferred Agents:** BOCEPREVIR CAPSULES (VICTRELIS®) PEGINTERFERONE ALFA-2B (PEGINTRON REDIPEN®), PEGINTERFERON ALFA-2B (PEGINTRON®) KIT, RIBAVIRIN CAPSULES AND TABLETS, TELAPREVIR (INCIVEK®) TABLETS
- **Non-Preferred Agents:** PEGINTERFERON ALFA-2A (PEGASYS PROCLICK®, PEGASYS®), RIBAVIRIN DOSE-PACK (RIBAPAK®)

Current PA: Prior authorization criteria is currently in place for oral protease inhibitors (Appendix 1) to ensure that they are used in appropriate patients and in consultation with a hepatologist, and for pegylated interferons and ribavirins (Appendix 2) to support preferred alternatives.

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:

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

Recommendations:

- There are multiple new drugs in the pipeline that are expected to change the course of therapy. No further research or review needed until available.
- Recommend making peginterferon alfa-2a (Pegasys®) an alternative preferred pegylated interferon.

- Revise criteria #9 of current PA criteria (Appendix 1), requiring denial for patients with HIV coinfection and allow approval for patients with HIV/HCV co-infection if the patient is under supervision of an HIV specialist.

Previous Conclusions and Recommendation:

- Recommend to maintain either one or both of peginterferon alfa-2a (Pegasys®) and peginterferon alfa-2b (PegIntron®) as preferred pegylated interferon products. These two agents are recommended in the current guidelines and have been shown to be similar in efficacy and safety.
- Designate interferon alfacon-1 as a non-preferred agent due to the lack of recommendations for use in current treatment guidelines.
- Prior authorize the oral protease inhibitors (boceprevir [BOC] and telaprevir [TVR]) for use in patients with genotype 1 chronic hepatitis c in combination with pegylated interferon and ribavirin and other drug specific criteria (Appendix 1).

Methods:

A Medline literature search beginning August 2012 (since the most recent AHRQ report) and ending July 2013 for new systematic reviews and randomized controlled trials (RCTs) that compared antiviral regimens and oral protease inhibitors, including boceprevir (BOC) and telaprevir (TVR) 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:

1. An AHRQ comparative effectiveness review evaluated the comparative benefits and harms of current antiviral treatment regimens for chronic HCV in treatment-naïve adults.[1] A total of 90 RCTs and observational studies were included from a literature search up to August 2012. There was no direct evidence comparing current regimens on long-term clinical outcomes. However, results from 5 trials provided moderate strength evidence that SVR rates were substantially higher in patients with HCV genotype 1 infection who were on triple therapy with pegylated interferon, ribavirin, and an oral protease inhibitor (boceprevir or telaprevir) compared with dual therapy with pegylated interferon plus ribavirin (absolute increase in SVR rates of 22-31%). Triple therapy with boceprevir was associated with increased risk of hematological effects while therapy with telaprevir was associated with an increased risk of anemia and severe rash compared to dual therapy. There was insufficient evidence to compare effectiveness of triple therapy to dual therapy based on fibrosis state.

   There was a difference in absolute SVR of about 8%, and moderate strength evidence of a slightly lower chance of achieving an SVR with dual therapy with pegylated interferon alfa-2b compared to dual therapy with pegylated interferon alfa- 2a (pooled RR 0.87, 95% CI 0.80 to 0.95; I2=27.4%). The largest study found no difference in SVR rates for dual therapy between the interferons. There was no difference in risk of withdrawals due to adverse events, but dual therapy with interferon alfa-2b was associated with a lower risk of serious adverse events than dual therapy with interferon alfa-2a (pooled RR 0.76, 95% CI

0.71 to 0.88; I2=0.0%). A large cohort study found that patients who achieved an SVR had a lower risk of all-cause mortality than patients who did not (Hazard ratio ranging from 0.51 to 0.71, depending on genotype).

2. The DynaMed review[2] notes that for patients with genotype 1, optimal therapy is protease inhibitor (boceprevir or telaprevir) plus peginterferon alfa and ribavirin based on increased virologic response rates. The same level of evidence is given for both protease inhibitors. It cites level 3 (low) evidence that boceprevir is as effective as telaprevir for reducing relapse and improving SVR when used with peginterferon alfa plus ribavirin.

3. A meta-analysis evaluated for the efficacy and tolerability of TVR in genotype 1 HCV.[3] Five RCT's evaluating TVR with peginterferon-alfa2b and ribavirin were identified and included. Trials were assessed for quality using the Cochrane methodology and the included trials generally were at a low risk of bias. The pooled estimates showed that the proportion of patients achieving SVR was significantly higher in the TVR group than the dual therapy group (OR 3.40; 95% CI 1.92-6.00, p<00001, I^2 =87%).[3] This was true for both the previously untreated subgroup (OR 2.25, 95% CI 1.35-3.77; p=0.002; i^2=77%) and in the previously treated subgroup (OR 6.70, 95% CI 3.35-13.41; p<0.002, I^2=71%). In addition, the incidence of drug discontinuations due to adverse events was significantly higher in the TVR group (OR 2.24, 95% CI 1.43-3.50; p<0.001; I^2=37%), with the most common being rash and anemia. This review included a small number of trials with significant heterogeneity. [3]

4. Another meta-analysis of RCTs compared the efficacy and safety of the addition of TVR to a standard regimen of peginterferon and ribavirin to the standard regimen alone.[4] Six RCTs were included in this meta-analysis and assessment of study quality was done using the Jadad system. Significant heterogeneity was observed between the included studies (I^2=80.5%, p<0.001). Overall, there was a significantly greater SVR rate in the TVR group compared to the standard group (66.5% vs. 35.8%, respectively, OR 3.81, 95% CI 2.43-5.96). This was similar in the subgroup of previously treated patients (OR 8.17, 95% CI 5.61-11.92) and untreated (OR 2.90, 95% CI 2.36-3.56). [4]

5. An indirect comparison of TVR and BOC in treatment-naïve and treatment-experienced genotype 1 CHC patients was conducted, using a Bayesian network meta-analysis framework.[5] A literature review identified all RCTs through July 2011; no head to head trials were available. Each trial was assessed for quality using the Cochrane metholodogy. A total of 11 studies were of acceptable quality and included in the meta-analysis. The analysis showed both BOC (OR 2.99; 95% CI 2.23-4.01) and TVR (3.80; 95% CI 2.78-5.22) to be superior to conventional dual therapy. Based on indirect comparisons, a meta-analysis suggests better efficacy for TVR than BOC in both treatment-naïve (OR 1.42, 95% CI 0.89-5.22) and treatment-experienced patients (OR 2.45; 95% CI 1.02-5.80). [5]

6. A systematic review with indirect comparisons included 13 RCTs evaluating direct-acting protease inhibitors in patients with HCV genotype 1 infection.[6] Six trials evaluated pegylated interferon alfa-2a plus ribavirin vs. pegylated interferon alfa-2b plus ribavirin. Three trials compared TVR plus peginterferonalpha-2a plus ribavirin to pegineterferon alfa-2a plus ribavirin and 4 trials compared BOC plus peginterferon alpha-2b plus ribavirin to opeginterferon alpha-2b plus ribavirin. Using indirect comparisons, TVR and BOC were statistically comparable in achieving SVR (OR 1.11; 95% CI 0.23-5.68) and relapse (OR 1.09; 95% CI 0.19-4.83). In treatment-experienced patients TVR and BOC were also comparable in achieving SVR (OR 1.45; 95% CI 0.70-3.08), relapse (OR 0.35; 95 % CI 0.13-1.02), and in discontinuations due to adverse events (OR 0.44; 95% CI 0.11 to 1.63). Triple therapy with either BOC or TVR achieved higher SVR rates, lower relapse rates, and higher discontinuation rates than dual therapy. There was a higher incidence of rash in patients treated with TVR compared with BOC (OR 3.09; 95% CI 1.45-6.65) and for treatment-experienced patients, all adverse event rates were higher with TVR.

7. Another mixed treatment comparisons looked at the differences in efficacy between BOC and TVR in the treatment of HCV genotype 1.[7] A literature search up to September 2012 identified 10 studies, 6 in treatment-naïve patients and 4 in treatment-experienced. Most of the studies had a low risk of bias. In treatment-naïve patients, there was insufficient evidence to detect a difference between TVR and BOC (OR 1.06, 95% CI 0.75-1.47). In the overall treatment experienced population (n=1495), there was also insufficient evidence to detect a difference in SVR between the two agents when added to standard of care (OR 1.27, 95% CI 0.71-2.30). When including only those patients with a prior treatment relapse (n=841), there was a significant difference in efficacy, favoring TVR (OR 2.61, 95% CI 1.24-5.52).

8. A meta-analysis evaluated if there were any differences in dual therapy with peginterferon alfa-2b vs. peginterferon alfa-2a in SVR, relapse, and treatment discontinuation.[8] Twenty-one trials were included for peginterferon alpha-2a plus ribavirin and fourteen trials included peginterferon alpha-2b plus ribavirin. Five were direct head-to-head evaluations. Among treatment naïve patients, the pooled estimate of SVR was 47% for those treated with peginterferon alpha-2a plus ribavirin and 40% for peginterferon alpha-2b plus ribavirin. For treatment-experienced patients, 12% on peginterfron alpha-2a achieved a SVR compared to 16% on peginterferon alpha-2b. The subgroup of head-to-head trials showed no significant differences between the two treatments.

9. Another meta-analysis of RCTs was performed to evaluate the efficacy and tolerability of peginterferon alfa-2a and peginterferon alfa-2b, both plus ribavirin.[9] A literature search through August 30, 2012 included 7 trials after review and exclusion. The methodological quality of the studies was assessed according to the Cochrane Collaboration's tool. In total, 1845 and 1823 patients were randomly treated with peginterferon alfa-2a and peginterferon alfa-2b, respectively. The overall SVR rates for patients treated with peginterferon alfa-2a plus ribavirin were 46.7% compared to 42.4% of patients treated with peginterferon alfa-2b (OR 1.20, 95% CI 1.04-1.38, p=0.01). A subgroup analysis found that SVR rate was significantly higher in the peginterferon alfa-2a group compared to peginterferon alfa-2b in treatment naïve patients (47.9% vs. 43.5%, OR 1.20, 95% CI 1.04-1.39, p=0.01). Meta-analysis by a random-effects model revealed similar discontinuation rates, while meta-analysis by a fixed-effects model demonstrated that peginterferon alfa-2a had a significantly lower discontinuation rate than peginterferon alfa-2b (27.9% vs. 33.9%, OR 0.71, 95% CI 0.61-0.84; p<0.0001).

10. A meta-analysis of data from 22 phase II and III trials compared 24 and 48 week SVR and adverse events between TVR and BOC regimens in the treatment of chronic HCV.[10] Both agents were compared to control therapy (peginterferon plus ribavirin) and indirectly compared to each other in a simple pairwise comparison. The indirect comparison favored TVR for 24-233k SVR in treatment-naïve patients (OR 1.78, 95% CI 1.39-2.28; p<0.0001) but there was no difference at 48 weeks (OR 0.82, 95% CI 0.6-1.11; p=0.2). TVR and BOC were similar in discontinuations due to adverse events (OR 1.23, 95% CI 0.95-1.6; p=0.11). Both agents showed improved SVR compared to dual therapy while increasing adverse events. [10]

New drugs/formulations/indications:
None

Horizon Scan:
A recent AHRQ Horizon Scan report identified 10 antiviral agents that are currently in Phase III trials for the treatment of chronic HCV.[11] Many of these agents are being studied as an interferon-free regimen and many have been granted fast-track status by the FDA. In particular, the drug sofosbuvir, is expected to have

high potential to address significant unmet needs for HCV treatment due to its high efficacy and being well-tolerated, as well as a shorter and simpler dosing regimen.[12] In June of this year, FDA granted sofosbuvir priority review with a Prescription Drug User Fee Act date of December 8, 2013. [12]

New FDA Safety Alerts:

In December 2012, the FDA released a drug safety communication of reports of serious skin reactions, some fatal, in patients taking telaprevir in combination with peginterferon and ribavirin.[13] Some patients died when they continued treatment after developing a worsening, or progressive rash and systemic symptoms. A boxed warning was added to the drug label that telaprevir combination treatment must be immediately stopped in patients experiencing a rash with systemic symptoms or a progressive severe rash.

New Guidelines:

The World Gastroenterology Organization updated their guideline on diagnosis, management and prevention of hepatitis.[14] The following are the main recommendations:

- All chronic hepatitis C patients with compensated liver disease should be considered for treatment.
- Treatment is strongly recommended for patients with moderate to advanced fibrosis
- Patients with mild disease should be considered for treatment on an individual basis, taking into account their age, gender, metabolic syndrome, symptoms, and motivation.
- Naïve CHC HCV genotype 1 patients with non-CC +Il28B and fibrosis F3-F4 should be treated with triple therapy for 48 weeks.
- Naïve patients with CC genotype IL28B and f1-f2 receive standard of care greamtnet (dual therapy) for 48 weeks, achive the same SVR rate.
- Special caution is needed in the treatment of patients with clinically apparent cirrhosis. Triple therapy is poorly tolerated and is associated with a 2% mortality rate.
- All patients in whom dual therapy treatment has failed, relapsers, partial responders, and null responders should be treated with triple therapy.

The U.S. preventive Services Task Force (USPSTF) recommend screening for HCV infection in persons at high risk for infection.[15] They also recommend offering 1-time screening for HCV infection to adults born between 1945 and 1964 (B recommendation). This recommendation came from 2 AHRQ systematic reviews used to update the screening recommendations. These reviews focused on evidence gaps identified in the previous recommendations.

The Department of Veterans Affairs (VA) Hepatitis C Resource Center Program/National Hepatitis C Program Office (HCRC/HCV) updated the recommendations on management and treatment of hepatitis C virus infection.[16] A grading system for recommendations was adapted from the AASLD guidelines. Major recommendations are as followed:

- IL28B genotype testing can be performed before pegylated interferon plus ribavirin, with or without a protease inhibitor, if the information on the probability of treatment response or duration would alter treatment decisions (Class IIa, Level B).
- Peggylated interferon and ribavirin, in combination with boceprevir or telaprevir is the standard of care for most treatment-naïve genotype 1-infected patients (Class I, Level A).
- For patients who previously failed PegIFN – RBV, retreatment with BOC or TVR, and PegIFN – RBV may be considered, particularly in patients who were relapsers (Class I, Level A).

- PegIFN alfa and RBV doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin, or platelets, as outlined in **Table 5** (Class I, Level A).
- If RBV is stopped for 7 days or more in patients who are concomitantly receiving BOC or TVR, then the PI also should be permanently discontinued (Class I, Level A).
- HCV PIs should be either continued at full dose or discontinued (Class I, Level A).
- Initial management of HCV treatment-related anemia should consist of RBV dose reduction in a symptomatic patientwith a hemoglobin < 10g/ dl, or as clinically indicated. Erythropoietin may be administered in patients with symptomatic anemia related to PegIFN – RBV therapy with or without BOC / TVR to limit anemia-related RBV dose reductions or dose disconinuations (Class II, LEVEL C)
- Initial management of HCV treatment-related neutropenia should consist of PegIFN dose reduction for an ANC < 750, or as clinically indicated. Granulocyte colony-stimulating factor should not be given as primary therapy to prevent PegIFN alfa dose reductions (Class I, Level C).

Guidance from NICE[17] recommends telaprevir in combination with peginterferon alfa and ribavirin as an option for genotype 1 CHC in adults with compensated liver disease:

- Who are previously untreated OR
- In whom previous treatment with interferon alfa alone or in combination with ribavirin has failed, including relapsers, partial responders, or non-responders.

Guidance from NICE[18] recommends boceprevir in combination with peginterferon alfa and ribavirin as an option for genotype 1 CHC in adults with compensated liver disease:

- Who are previously untreated OR
- In whom previous treatment has failed

Randomized Controlled Trials: A summary of the identified trials are in Table 1 below.

Study	Comparison	Population	Primary Outcome	Results
Flamm et al.[19] DB,RCT	BOC + pegenterferon alfa-**2a** + ribavirin vs. peginterferon alfa-2a + ribavirin	Adults with genotype-1 HCV with previously responsiveness to peginterferon and ribavirin but failure to achieve SVR N=201	SVR at 24 weeks	<u>% achieving SVR</u> BOC: 64% Peg/rib: 21% P<0.0001 Similar results as previous studies using BOC in combination with peginterferon alfa-2b
Gane et al.[20] Randomized, open-label	Sofosbuvir + ribavirin x 12 weeks vs. sofosbuvir + ribavirin + 4 wk, 8wk, or 12 wk of peginterferon	19 years or older Chronic HCV w/o cirrhosis Genotype 1, 2, and 3 N=95	SVR at 24 weeks	The presence or absence of peginterferon alfa-2a appeared to have no effect on rate of SVR

	alfa-2a				
Kowdley et al[21] Randomized, open-label	Sofosbuvir 200mg/day vs. sofosbuvir 400mg/day vs. placebo	18-70 years with previously untreated CHC (genotype 1)	SVR at 24 weeks	SVR at 12 weeks 90% (p=0.001) 91% (p=0.0005) 58%	
Sulkowski et al.[22] Subanalysis of Sprint-2[23]	BOC + peginterferon + ribavirin who developed anemia vs. those who did not develop anemia	Previously untreated patients with chronic HCV genotype 1 N=1097	Relationship between SVR and treatment-associated anemia and its management	SVR rate Anemia: 72% No anemia: 58%	SVR based on anemia management: EPO: 74% RBV Reduction: 72% Both: 70% Neither: 73%

Use in HIV/HCV co-infection:

Background: There is a significant overlap in the epidemiology of and risk factors for HIV and HCV infections. Patients with a new diagnosis of HIV infection may benefit from HIV antiretroviral therapy. Progression of liver disease is accelerated in patients with HIV/HCV co-infection and early antiretroviral therapy should be considered. HIV/HCV co-infection increases the risk of HCV related liver damage, may influence the duration of HCV therapy and lowers the likelihood of SVR. Before the availability of the direct acting antivirals (DDAs), practice guidelines recommended that HCV treatment should be given to patients with both HCV and HIV in whom the likelihood of serious liver disease and achieving SVR outweighs the risk for adverse events.[24] However, at the time of FDA approval and the drafting of major guidelines, the safety and efficacy of the DAA's had not been established in HIV/HCV coinfected patients, leading to a lack of consensus about their use in this population.[25] Challenges to the use of these agents in patients with HIV/HCV coinfection include drug-drug interactions, additional drug toxicities, and the need for therapy with interferon alfa. Limited data indicate that HCV protease inhibitors may increase the SVR rate, with manageable toxicity and drug-drug interactions and currently the 2 direct acting antivirals only have approved indications for the treatment of patients with genotype 1 HCV monoinfection.

It is important to evaluate a patient's fibrosis level to determine the most appropriate treatment approach in HIV/HCV coinfected individuals. Treatment-naïve patients with no evidence of fibrosis can typically defer treatment, while patients with F2/3 fibrosis should receive therapy with protease inhibitor-based triple therapy. Because novel HCV treatment regimens are expected in 2014, some clinicians recommend deferral of HCV treatment in HIV/HCV-coinfected patients with minimal hepatic fibrosis.[25]

Telaprevir: One published phase IIa RCT evaluated the safety and efficacy of 12 weeks of TVR plus pegylated interferon alfa and ribavirin, followed by 36 weeks of peginterferon and ribavirin in 60 patients with genotype 1 HCV and HIV.[24] Patients were treated for a total of 48 weeks regardless of achieving an undetectable HCV RNA during TVR therapy. Patients were required to be on either no antiretrovirals or 1 or 2 specific regimens (either efavirenz or ritonavir-

boosted atazanavir, based on pharmacokinetic studies). On the basis of drug interaction studies, patients receiving efavirenz-based therapy received 1125 mg of TVR every 8 hours, as compared to the standard dose of 750 mg every 8 hours. A total of 60 patients with stable HIV disease and who had no previous HCV treatment were randomized to TVR or placebo. Thirteen of these patients did not receive antiretroviral therapy, and 47 received efavirenz-containint (n=24) or ritonavir-boosted, atazanavir-containint (n=23) antiretroviral therapy. [24]

Of the 60 patients, 35 (58%) completed 48 weeks of treatment and 25 (42%) discontinued treatment early because of a virologic failure; this significant attrition reduces the quality of the study. SVR was achieved in 74% of patients in the TVR group compared to 45% in placebo. By week 4, HCV RNA levels were not detected in 68% of TVR patients compared to 0% in the placebo group. By week 12, 79% in the TVR group achieved undetectable HCV RNA, compared to 27% in the placebo group. More patients in the TVR group had pruritus, headache, nausea, rash, and dizziness compared to placebo. Overall, adverse events were similar to those seen in studies in patients with only HCV and no adverse impact on HIV disease parameters was observed. The small number of patients in this study and appreciable dropout rate result in the need for larger phase III studies evaluating the safety and efficacy of TVR in patients with HCV/HIV coinfection. In addition patients with more advanced HIV infection and who had been previously treated for HCV were not included in the study, decreasing the generalizability of the results. AS a result of this, larger phase III studies are currently ongoing.[25]

Boceprevir: In a phase II study, BOC versus placebo in combination with pegylated interferon and ribavirin were evaluated in 98 patients with HCV genotype 1 and HIV.[26] Like the previous trial, only adults with stable HIV disease and untreated HCV were included in the study population. A total of 65 patients were randomized to the BOC group and 34 to the placebo group. Forty patients (40%) discontinued treatment early; most due to treatment failures in the control group and adverse events in the BOC group.

Most patients had an HIV RNA viral load of less than 50 copies per ml and most were taking a ritonavir-boosted protease inhibitor with two nucleoside reverse-transcriptase inhibitors. 85% of patients had minimal to no fibrosis (F0-2 fibrosis score), and only 6 (9%) had advanced fibrosis. More patients in the BOC group achieved SVR at week 24 compared to placebo (63% vs. 29%, respectively, p=0.0008). For patients who were missing data at week 24, responses at week 12 were imputed. Efficacy of BOC seemed similar across specific HIV protease inhibitors. Thirteen (20%) patients in the BOC group discontinued due to an adverse event compared to 3 patients (9%) in the control group. HIV breakthrough occurred in 3 patients in the BOC group and 4 patients on placebo. Larger, phase III trials are in progress.

Guidelines:

The US Department of Health and Human Services (DHHS) 2012 update contain preliminary recommendations on the use of boceprevir and telaprevir in HIV-0infected patients with genotype 1 HCV.[27] The guidelines suggest the following:

- Either boceprevir or telaprevir can be used if the patient is not receiving and does not require antiretroviral therapy.
- A patient on raltegravir and 2 nucleoside reverse transcriptase inhibitors (NRTIs) can be treated with either HCV DAA.
- A patient receiving ritonavir-boosted atazanavir and 2 NRTIs can receive standard-dose telaprevir, but boceprevir should not be used
- Patients receiving efavirenz plus 2 NRTIs can receive telaprevir for HCV treatment at an increased dose of 1125 mg every 7-9 hours
- Boceprevir should not be coadministered with efavirenz

The European AIDS Clinical Society (EACS)[28]:

- Treatment can be deferred in the following patients:
    - Those with the lack of or minimal liver fibrosis (F0-1)
    - Patients with low chances of SVR for whom improved treatment options will become available within the coming years
    - Patients with expected adherence issues where it appears advisable to defer treatment until easier to take, better tolerated DAAs become available.
- Protease inhibitor-based therapy with either boceprevir or telaprevir is now the standard of treatment in HCV genotype infection in HIV-infected individuals where available.
- Due to drug drug interactions, telaprevir can only be safely combined with boosted atazanavir, raltegravir, rilpivirine, etravirine or efavirenz in combination with tenofovir or abacavir and FTC or 3TC.
- There is no data in HIV/HCV treated subjects that shorter treatment durations of triple therapy are efficacious
- Due to drug drug interactions, boceprevir can only be safely combined with raltegravir or etravirine in combination with tenofovir or abacavir and FTC or 3TC.

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Appendix 1: PA criteria

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 6-10 weeks (depending on regimen)
- Continuation of therapy up to 48 weeks of total therapy

Requies PA:

- Telaprevir
- Boceprevir

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 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 #4	**No:** Pass to RPh, Deny For Appropriateness
4. Is the request for continuation of therapy? (Patient has been on triple therapy with a oral antiviral agent in preceding 6 weeks)	**Yes**: Go to "Continuation of Therapy	**No**: Go to #5
5. Does the patient have a Child-Pugh score < 7 (compensated liver disease)?	**Yes:** Go to #6	**No:** Pass to RPh, Deny For Appropriateness
6. 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 #7	**No:** Pass to RPh, Deny For Appropriateness
7. If the patient has been treated with peginterferon and ribavirin before, do they have documented compliance/adherence to their previous treatment?	**Yes:** Go to #8	**No:** Pass to RPh, Deny For Appropriateness
8. Does the patient have a biopsy to indicate moderate to severe fibrosis (stage 2 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins).	**Yes:** Go to #9	**No:** Pass to RPh, Deny For Appropriateness
9. Does the patient have a HIV coinfection?	**Yes:** Go to #10	**No:** Go to #11

10. Is the patient under the supervision of an HIV specialist?	**Yes:** Go to #11	**No:** Pass to RPh; Deny (medical appropriateness)
11. Has the patient previously been treated with boceprevir or telaprevir?	**Yes**: Pass to RPh, Deny for appropriateness	**No:** Go to #12
12. Is the request for telaprevir 750mg (two tabs) TID for 12 weeks?	**Yes:** Approve for 6 weeks to allow for 4 week viral load check to continue for a maximum of 12 weeks	**No:** Go to #13 (If dose is different pass to RPh for appropriateness)
13. 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 10 weeks to allow for 8 week viral load check to continue for a maximum of 24, 32, or 40 weeks based on response	**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 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)
***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.		

Appendix 2: Interferon/ribavirin PA criteria

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? 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.	**Yes:** Forward to DMAP Medical Director	**No:** Go to #7
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	**Yes:** Deny; Pass to RPH (Medical Appropriateness)	**No:** Go to #8

• hemoglobinopathy • untreated hyperthyroidism • severe renal impairment or transplant • autoimmune disease • pregnancy • unstable CVD		
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).

Continuation of Therapy- HCV

<table>
<tr>
<td>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?</td>
<td>Yes: Approve as follows:

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

<table>
<tr><th>Genotype</th><th>Approve for</th><th>Apply</th></tr>
<tr><td>1 or 4</td><td>An additional 36 weeks or for up to a total of 48 weeks of therapy (whichever is the lesser of the two).</td><td>Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose =1200 mg).</td></tr>
<tr><td>2 or 3</td><td>An additional 12 weeks or for up to a total of 24 weeks of therapy (whichever is the lesser of the two).</td><td>Ribavirin quantity limit of 200 mg tab QS# 120 / 25 days (for max daily dose = 800 mg).</td></tr>
<tr><td>For all genotypes and HIV co-infection</td><td>An additional 36 weeks or for up to a total of 48 weeks of therapy (whichever is the lesser of the two)</td><td>Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose = 1200 mg).</td></tr>
</table>
</td>
<td>No: DENY
(Medical Appropriateness)

Treatment with pegylated interferon-ribarvirin does not meet medical necessity criteria because there is poor chance of achieving an SVR.</td>
</tr>
</table>

Clinical Notes:

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

Stage is indicative of fibrosis:			**Grade is indicative of necrosis:**	
Stage 0	No fibrosis			
Stage 1	Enlargement of the portal areas by fibrosis		Stage 1	None
Stage 2	Fibrosis extending out from the portal areas with rare bridges between portal areas		Stage 2	Mild
Stage 3	Fibrosis that link up portal and central areas of the liver		Stage 3	Moderate

Stage 4	Cirrhosis		Stage 4	Marked

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

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