Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | **Fax** 503-947-1119

Abbreviated New Drug Evaluation: Simeprevir

Month/Year of Review: January 2014
New Drug: Simeprevir **(**Olysio®)
Dossier Received: Pending

End of literature search: September 2013
Manufacturer: Janssen Therapeutics

FDA Approved Indication: Simeprevir is a hepatitis C virus (HCV) protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen.[1]

- Simeprevir efficacy has been established in combination with peginterferon alfa and ribavirin in HCV genotype 1 infected subjects with compensated liver disease (including cirrhosis).
- Simeprevir must not be used as monotherapy.
- Alternative therapy should be considered for patients infected with HCV genotype 1a containing he Q80K polymorphism.

Research Questions:

- Is there any evidence that simeprevir is effective for the treatment of CHC in reaching sustained virologic response (SVR) or reducing mortality and the development of long term clinical outcomes such as hepatocellular carcinoma?
- Is there evidence demonstrating the safety of simeprevir in the treatment of CHC?
- Is there any comparative evidence demonstrating superior efficacy or safety of simeprevir compared to other protease inhibitors?
- Are there subpopulations of patients for which simeprevir is more effective or associated with less harm?

Conclusions:

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 Most of the data remains unpublished and cannot be assessed for quality.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

- There is insufficient evidence evaluating the use of simeprevir in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).The combination of simeprevir should not be used in patients with decompensated cirrhosis (moderate to severe hepatic impairment).
- There is low quality evidence of an increased risk of adverse reactions in patients of East Asian ancestry due to higher simeprevir exposure.

Recommendations:

- Apply Hepatitis C Protease Inhibitor/Triple Therapy prior authorization criteria and limit use to:
  - Patients with HCV genotype 1
  - Without the Q80K polymorphism virus
  - Patients also on peginterferon alfa and ribavirin
  - Compensated liver disease
  - Prescribed by or in consultation with a hepatologist
- Bring back more detailed review and quality assessment of the evidence for further decision-making.
- Review report of Community Hepatitis workgroup.

Reason for Review: Two new drugs indicated for the treatment of CHC have recently been approved. This review will evaluate the evidence for efficacy and safety of simeprevir and determine its place in therapy.

Methods:

A MEDLINE OVID search was conducted using simeprevir for chronic Hepatitis C or Hepatitis C virus and limited to randomized controlled trials (RCTs) and meta-analysis, English language, and conducted in humans. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality 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. From the literature search, two phase 2 studies were identified.[2,3] One open-label pharmacokinetic study was excluded due to study design.[4] No published phase 3 studies were available at the time of this report.

Background:

Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma.[5] 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.[5] 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.

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.[5] Current standard of care for Genotype 1 CHC is a protease inhibitor (boceprevir or telaprevir) plus pegylated interferon and ribavirin.[6] This is based on several RCTs showing improved rates of SVR (63-79%) with triple therapy compared to

Author: Megan Herink, Pharm.D.

the previous standard of care of pegylated interferon and ribavirin dual therapy (55-60%). There is no direct comparative evidence on the effectiveness of the currently available protease inhibitors. However, these agents come with several safety concerns and still depend on combination therapy with interferon and ribavirin which also include adverse reactions an increased risk of anemia and rash sometimes require premature treatment discontinuation and additional management, adding to the complexity of treatment. [7] There are also important drug interactions seen with these protease inhibitors. For genotypes 2 and 3, the standard of care is still dual therapy with pegylated interferon and ribavirin for 24 weeks, which has shown SVR rates of 71-75% in genotype 2 and 61-66% in genotype 3.[8]

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

Clinical Trials:

Efficacy

Simeprevir has been studied in two fair quality phase 2 trials[2,3] and three Phase 3 trials.[1, 6] None of the phase III trials have been published and therefore cannot be assessed for quality. Two double-blind, placebo-controlled phase 2b studies were provided in support of the proposed indication that were designed to evaluate various doses and durations of therapy, one in treatment-naïve patients and one in treatment-experienced patients. Study C205 (n=388) was a randomized, double-blind, placebo-controlled trial to evaluate simeprevir 75 and 150 mg daily given for either 12 or 24 weeks in treatment-naïve CHC genotype 1 subjects.[2] This was compared to placebo (for 24 weeks) in combination with peginterferon and ribavirin for 48 weeks. The second phase 2b trial (C206) also compared the safety and efficacy of different regimens of simeprevir (100 or 150 mg daily) plus peginterferon and ribavirin in CHC genotype 1 subjects who had failed to respond during or had relapsed following at least 1 course of dual therapy for various durations (12 weeks, 24 weeks, or 48 weeks).[3] The primary endpoint was SVR at weeks 72 and 24. Patients with cirrhosis and co-infected with HIV were excluded from the studies. Most patients were Caucasian males with a median age of 46.5 years. In study C205, SVR at week 72 ranged from 70.7% to 84.8% compared with 64.9% for those on dual therapy ($p<0.05$). The study was designed to evaluate two different doses and two different durations of triple combination therapy. All four treatment arms accomplished similar rates of SVR (75% to 86%) which were statistically significantly higher than placebo in all but one of the 75 mg treatment groups. In study C206, SVR at week 24 was achieved in 60.6%-80% of simeprevir groups compared to 22.7% in placebo ($p<0.001$). SVR was achieved in more patients in the 150 mg group compared to 100 mg group (72.9% vs. 65.5%) and similar results were seen for those receiving 12 weeks, 24 weeks, and 48 weeks of triple therapy (68.2%, 69.2%, and 70.2%, respectively). SVR rates in patients with a prior null response (41.2%-58.8%), partial response (65.2%-86.4%), and relapse (76.9%-88.9%) were also promising. In a pooled analysis, the difference in SVR24 rates between simeprevir groups and placebo in partial responders reached statistical significance ($p<0.0001$) and did not reach statistical significance in null responders (45% vs. 19%, $p=0.11$).

The phase 3 trials were randomized, double-blind, placebo controlled trials in subjects with HCV genotype 1.[7] They evaluated the combination of simeprevir 150 mg daily for 12 weeks plus peginterferon-alpha and ribavirin for 12 weeks followed by peginterferon alpha and ribavirin alone for either 12 or 36 weeks based on virologic response compared to placebo in combination with peginterferon alpha and ribavirin for a fixed 48 week duration. The primary endpoint was SVR 12 weeks after the end of treatment. Two trials enrolled only treatment-naïve subjects and the third enrolled subjects who had received at least 24 weeks of a

pegylated interferon-based therapy and had relapsed within 1 year (relapsers). According to the FDA, demographic characteristics were generally well balanced in the phase 3 trials. The majority of subjects were Caucasian (86-96%). Cirrhotic subjects (Metavir Fibrosis score of F4) comprised from 7 to 15% of subjects across study arms.

The pooled results from the two trials in treatment naïve subjects resulted in a 80% SVR in the treatment group compared to 50% in placebo ($p < 0.001$ for both trials). In the trial of relapsers, 79% of subjects receiving treatment reached an SVR compared to 36% in placebo ($p<0.001$). SVR rates at weeks 24 and 72 correlated well with the primary SVR12 endpoint. In subgroup analysis, no statistically significant differences in SVR rates were observed in those with the Q80K polymorphism at baseline (58% vs. 55%) between the simeprevir and control arms. The Q80K polymorphism is a common polymorphism found in genotype 1 patients. Given the high frequency in the U.S. population and its significant impact on rates of SVR12, the drug advisory committee recommended that all genotype 1a patients be screened for the Q80K polymorphism and alternative treatment options should be considered for patients found to be infected with this variant. This was also similar in the trial including relapsers (47% vs. 30%). In all other subgroup analyses, SVR rates were significantly higher in the simeprevir group compared to the control group.

A secondary endpoint of the phase 3 studies was the proportion of patients able to shorten total treatment duration to 24 weeks. In the triple therapy groups, 85% and 91% of the treatment-naïve patients, and 93% of the prior relapse patients were eligible for a shortened total treatment duration with peginterferon and ribavirin from 48 to 24 weeks.

Safety:

A total of 1178 subjects who received simeprevir or placebo in clinical trials contribute to the safety data available at this time. The most common adverse events seen in clinical trials were rash (28%), pruritus (22%), nausea (22%), influenza like illness (26%), and myalgia (16%), and photosensitivity. Adverse reactions that occurred with at least 3% higher frequency among subjects receiving simeprevir compared to placebo are included in the table below:

Adverse Reaction	**Simeprevir + Peginterferon alfa+ Ribavirin N=781 % (n)**	**Placebo + Peginterferon alfa+ Ribavirin N=397 % (n)**
Rash (including photosensitivity)	28 (218)	20 (79)
Pruritus	22 (168)	15 (58)
Nausea	22 (173)	18 (70)
Myalgia	16 (126)	13 (53)
Dyspnea	12 (92)	8 (30)

*Adapted from Simeprevir prescribing information[1]

Discontinuations due to adverse reactions occurred in 2% of simeprevir treated subjects and 1% of placebo subjects. Dyspnea occurred in 12% of subjects in the simeprevir group and 8% in the control group. A greater frequency of adverse events associated with increased bilirubin was reported in the simeprevir group. It was known since its early development that hyperbilirubinemia was associated with the use of simeprevir, and occurred in 49% of simeprevir patients compared to 26% in the control group. Elevations occurred early after the initiation of treatment and levels returned to near baseline often by week 4 and there was no

Author: Megan Herink, Pharm.D.

observed clinically relevant hepatotoxicity associated with the increase. There were no reported causes of Stevens Johnson syndrome or toxic epidermal necroylsis, however an increase in serious adverse events and increase in rates of discontinuation due to rash/photosensitivity related events occurred. The proportion of patients who discontinued simeprevir treatment early was 6.7% in the treatment group and 66.5% in patients on placebo, mainly due to meeting the treatment stopping rule at week 4. During the first 12 weeks, 1.8% of the simeprevir treated patients and 1.3% of the patients on placebo discontinued due to an adverse event. Rash was the most common event leading to discontinuation of treatment in the simeprevir arm (0.6%).

References:

1. Simeprevir prescribing information. Titusville NJ : Janseen Therapeutics. November 2013.

2. Fried MW, Buti M, Dore GJ, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naïve genotype 1 hepatitis C: The randomized PILLAR study. *Hepatology*. 2013;58(6):1918–1929. doi:10.1002/hep.26641.

3. Zeuzem S, Berg T, Gane E, et al. Simeprevir Increases Rate of Sustained Virologic Response Among Treatment-Experienced Patients With HCV Genotype-1 Infection: A Phase IIb Trial. *Gastroenterology*. 2013. doi:10.1053/j.gastro.2013.10.058.

4. Hayashi N, Seto C, Kato M, Komada Y, Goto S. Once-daily simeprevir (TMC435) with peginterferon/ribavirin for treatment-naïve hepatitis C genotype 1-infected patients in Japan: the DRAGON study. *J Gastroenterol*. 2013. doi:10.1007/s00535-013-0875-1.

5. Chou R, Hartung D, Rahman B, Wasson N, Cottrell E, Fu R. *Treatment for Hepatitis C Virus Infection in Adults*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012. Available at: http://www.ncbi.nlm.nih.gov/books/NBK115347/. Accessed July 18, 2013.

6. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54(4):1433–1444. doi:10.1002/hep.24641.

7. Simeprevir (TMC435). FDA Antiviral Drugs Advisory Committee Meeting. October 24th, 2013. Background Packate for NDA 205123. Available at: http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CC4QFjAA&url=http%3A%2F%2Fwww.fda.gov%2Fdownloads%2FAdvisoryCommittees%2FCommitteesMeetingMaterials%2FDrugs%2FAntiviralDrugsAdvisoryCommittee%2FUCM371623.pdf&ei=8lGvUr-UMsWbygHIr4DoAw&usg=AFQjCNGsHT7v0WZNvYximPhkr9qgFSuhMw&sig2=fKXf_Fo7xTH1FcoXHlmxrQ&bvm=bv.57967247,d.aWc&cad=rja.

8. Chou R, Hartung D, Rahman B, Wasson N, Cottrell EB, Fu R. Comparative effectiveness of antiviral treatment for hepatitis C virus infection in adults: a systematic review. *Ann Intern Med*. 2013;158(2):114–123.

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Appendix 1: Current 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~~ 8-12weeks (depending on regimen)
- Continuation of therapy up to 48 weeks of total therapy

Requires PA:

- Telaprevir
- Boceprevir
- Simeprevir

Approval Criteria		
1. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:	**Yes:** Go to #2	**No:** Pass to RPh, Deny For Appropriateness
2. Does the patient have documented HCV genotype 1? Record Genotype:	**Yes:** Go to #3	**No:** Pass to RPh, Deny For Appropriateness
3. Is the prescription for simeprevir?	**Yes: Go to #4**	**No: Go to #6**
4. Has the patient been screened for the presence of virus with the NS3 Q80K polymorphism at baseline?	**Yes: Go to #5**	**No:** Pass to RPh, Deny For Appropriateness. Recommend that the screening take place.
5. Does the patient have the genotype 1 Q80K polymorphism virus?	**Yes:** Pass to RPh, Deny for Appropriateness	**No:** Go To #6
~~4.~~6. Is the patient also being prescribed peginterferon alfa-2a or -2b and ribavirin and has been granted prior authorization or meets criteria for pegylated interferon-alfa	**Yes:** Go to #74	**No:** Pass to RPh, Deny For Appropriateness

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and ribavirin?		
~~5.~~7. Is the request for continuation of therapy? (Patient has been on triple therapy with an oral antiviral agent in preceding 6 weeks)	**Yes**: Go to "Continuation of Therapy	**No**: Go to #~~8~~5
~~6.~~8. Does the patient have a Child-Pugh score < 7 (compensated liver disease)?	**Yes:** Go to #~~9~~6	**No:** Pass to RPh, Deny For Appropriateness
~~7.~~9. Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C?	**Yes:** Go to #~~10~~7	**No:** Pass to RPh, Deny For Appropriateness
~~8.~~10. If the patient has been treated with peginterferon and ribavirin before, do they have documented compliance/adherence to their previous treatment?	**Yes:** Go to #~~11~~8	**No:** Pass to RPh, Deny For Appropriateness
~~9.~~11. 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 #~~12~~9	**No:** Pass to RPh, Deny For Appropriateness
~~10.~~12. Does the patient have a HIV coinfection?	**Yes:** Go to #~~13~~0	**No:** Go to #11
~~11.~~13. Is the patient under the supervision of an HIV specialist?	**Yes:** Go to #~~14~~1	**No:** Pass to RPh; Deny (medical appropriateness)
~~12.~~14. Has the patient previously been treated with boceprevir, telaprevir, or simeprevir?	**Yes**: Pass to RPh, Deny for appropriateness	**No:** Go to #~~15~~2
~~13.~~15. Is the request for telaprevir 750mg (two tabs) TID for 12 weeks?	**Yes:** Approve for 8 weeks to allow for 4 week viral load check to continue for a maximum of 12 weeks	**No:** Go to #~~16~~3 (If dose is different pass to RPh for appropriateness)
~~14.~~16. Is the request for boceprevir 800mg (four tabs) TID and the patient has completed 4 weeks of lead-in treatment with ribavirin and peginterferon?	**Yes:** Approve for 12 weeks to allow for 8 week viral load check to continue for a maximum of 24, 32, or 40 weeks based on response	**No:** Go to #17 (If dose is different pass to RPh for appropriateness)~~Pass to RPh; Deny for appropriateness~~
17. Is the request for simeprevir 150 mg once daily for 12 weeks?	**Yes: Approve for 8 weeks to allow for 4 weeks viral load check to continue for a maximum of 12 weeks**	**No: Pass to RPh; Deny for appropriateness**

Continuation of Therapy- Telaprevir		
1. Is the patient treatment-naïve or a prior relapse patient and has undetectable HCV RNA or measured at 4 and 12 weeks?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.

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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

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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.		

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Continuation of Therapy- Simeprevir: Simeprevir in combination with peginterferon alfa and ribavirin should only be given for 12 weeks. No more simeprevir should be approved. The following are the recommended duration of treatments for dual therapy with peginterferon alfa and ribavirin after the initial 12 weeks of triple therapy		
1. Is the patient treatment-naïve or a prior relapse and has undetectable HCV RNA (< 25 IU/ml) at week 4?	**Yes:** Approve as follows: • Approve additional 4 weeks of simeprevir for total treatment duration of 12 weeks of triple therapy, followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks).	**No:** DENY (Medical Appropriateness) It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients.
2. Is the patient a prior non-responder (including partial and null responders) and has an undetectable HCV RNA (<25 IU/ml) at week 4?	**Yes:** Approve as follows: • Approve additional 4 weeks of simeprevir for total treatment duration of 12 weeks of triple therapy, followed by continued dual therapy with peginterferon and ribavarin for 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients
***TREATMENT FUTILITY RULES** If the patient has HCV-RNA results greater than or equal to 25 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue two-medicine regimen.		

Author: Megan Herink, Pharm.D.

Appendix 2: Specific Drug Information

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	Good oral bioavailability
Protein Binding	>99.9%, mainly albumin
Elimination	Predominantly in the feces via biliary excretion
Half-Life	41 hours
Metabolism	CYP3A enzymes

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
150 mg	PO	Q24H	150 mg once daily with food	No adjustment needed	A dose recommendation cannot be made for patients with moderate to	No information available..	No differences in safety, efficacy or response have been observed	• A dose recommendation cannot be made for patients of East Asian ancestry. • Should be administered with both peginterferon alfa and ribavirin.

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					severe hepatic impairment. Is contraindicated in patients with decompensated cirrhosis.		among patients of varying age. Skin changes with advanced age may lead to increased rug exposure.	The recommended duration of simeprevir is 12 weeks, followed by either 12 or 36 additional weeks of peginterfron alfa and ribavirin depending on prior response status. • For discontinuation, the daily dose should be reduced by 2mg/24 hours with a dose reduction preferably every other day, until complete withdrawal.

The recommended duration of treatment with simeprevir, peginterferon alfa and ribavirin is presented in the following table:

Duration of Treatment with OLYSIO, Peginterferon Alfa and Ribavirin			
	Treatment with simeprevir, Peginterferon alfa and Ribavirin*	**Treatment with Peginterferon alfa and Ribavirin***	**Total Treatment Duration***
Treatment-naïve and prior relapser patients† including those with cirrhosis	First 12 weeks	Additional 12 weeks	24 weeks
Prior non-responder patients‡ (including partial and null responders) including those with cirrhosis	First 12 weeks	Additional 36 weeks	48 weeks
* Recommended duration of treatment if patient does not meet stopping rule (see Table 2). † Prior relapser: undetectable HCV RNA at the end of prior interferon-based therapy and detectable HCV RNA during follow-up ‡ Prior partial responder: prior on-treatment ≥ 2 log10 IU/ml reduction in HCV RNA from baseline at Week 12 and detectable HCV RNA at end of prior interferon-based therapy. Prior null responder: prior on-treatment < 2 log10 reduction in HCV RNA from baseline at Week 12 during prior interferon-based therapy			

Stopping rules for simeprevir are presented here:

Treatment Stopping Rules in Any Patient with Inadequate On-Treatment Virologic Response	
HCV RNA	Action

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Treatment Week 4: greater than or equal to 25 IU/mL	Discontinue simeprevir, 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

DRUG SAFETY[1]

Contraindications: All contraindications to peginterfron alfa and ribavirin also apply to simeprevir combination treatment and is contraindicated in pregnant women and in men whose female partners are pregnant.

Warnings and Precautions:

- Embryofetal Toxicity (use with ribavirin). Ribavirin may cause defects and fetal death. Avoid pregnancy in female patients and female partners of male patients.
- Photosensitivity: serious photosensitivity reactions have been observed. Use sun protection measures and limit sun exposure. Consider discontinuation if a photosensitivity reaction occurs.
- Rash. Discontinue if severe rash occurs.

Drug Interactions:

- Co-administration with drugs that are moderate or strong inducers or inhibitors of CYP3A may significantly affect the plasma concentrations of simeprevir.

Look-alike/Sound-alike Potential:

Rotigotine may be confused with : *rasagiline, rivastigmine, ropinirole*
Neupro may be confused with: *Neupogen, Neurontin*

Author: Megan Herink, Pharm.D.