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

Abbreviated Class Update: Hepatitis C

Month/Year of Review: January 2014
New Drug: Sofosbuvir **(**Sovaldi®)
Dossier Received: Yes

End of literature search: September 2013
Manufacturer: Gilead Sciences

FDA Approved Indication: Sofosbuvir is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen.[1]

- The efficacy of sofosbuvir has been established in subjects with HCV genotype 1, 2, 3 or 4 infections, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection.

Research Questions:

- Is there any evidence that sofosbuvir 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 sofosbuvir in the treatment of CHC?
- Is there any comparative evidence demonstrating superior efficacy or safety of sofosbuvir compared to other protease inhibitors?
- Are there subpopulations of patients for which sofosbuvir is more effective or associated with less harm?

Conclusions:

- There is poor quality evidence, based on one open-label trial, that sofosbuvir in combination with ribavirin for 12 weeks is noninferior to pegylated interferon plus ribavirin for 24 weeks in genotype 2 and 3 treatment-naïve CHC in achieving SVR at week 12 (67% for both groups).[2]
- There is low quality evidence that sofosbuvir in combination with ribavirin for 12 weeks is superior to placebo in genotype 2 and 3 CHC patients who are intolerant or ineligible for interferon based therapy in achieving SVR at week 12 (78% vs. 0%; $p<0.001$), as well as in patients who did not have a response to interferon therapy.[3]
- There is evidence that extending the duration of treatment in genotype 3 patients to 24 weeks improves SVR rates compared to 12 weeks of treatment. Across all studies, genotype 2 patients achieved consistently higher SVR rates than genotype 3 patients
- In genotype 1, there low quality to insufficient evidence that the combination of sofosbuvir plus ribavirin plus peginterferon alfa results in higher rates of SVR at 12 weeks than historical control rates (90% vs. 60%). This is based on a single arm, poor quality open-label study. [2]
- Based on limited data, sofosbuvir appears to have no serious adverse event concerns associated with its use and is well-tolerated for 12-16 weeks. The most common adverse events (>20%) of sofosbuvir in combination with ribavirin were fatigue and headache. The most common adverse events in combination with peginterferon alfa and ribavirin were fatigue, headache, nausea, insomnia, and anemia. Overall discontinuations due to adverse events in trials were low (0-2%). Longer term and larger trials are needed to fully assess safety issues associated with sofosbuvir.

Recommendations:

- Implement initial and preliminary PA criteria limiting use to:
  - Patients also on peginterferon and ribavirin with HCV genotype 1 or 4
  - Patients also on ribavirin with HCV genotypes 2 and 3
  - Prescribed by or in consultation with a hepatologist
  - Has evidence of moderate to severe fibrosis
- Bring back to March P&T to develop more specific and detailed PA criteria
- 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 the effectiveness and safety of sofosbuvir and determine its appropriate place in therapy.

Background:

Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma.[4] 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. [4] 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.[5]

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. [4] 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 the previous standard of care of pegylated interferon and ribavirin dual therapy (55-60%). There is no direct comparative evidence on the effectiveness of the currently available protease inhibitors. However, these agents come with several safety concerns and still depend on combination therapy with interferon and ribavirin which can result in serious adverse reactions. There are also important drug interactions seen with these protease inhibitors. For genotypes 2 and 3, the standard of care is still dual therapy with pegylated interferon and ribavirin for 24 weeks, which has shown SVR rates of 71-75% in genotype 2 and 61-66% in genotype 3.[7]

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.[5] 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.

Author: Megan Herink, Pharm.D.

Methods:
A MEDLINE OVID search was conducted using sofosbuvir 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, three phase 2 studies[8–10] and four phase 3 published studies were identified.[2,3] One open-label study was excluded due to study design.[11]

Clinical Trials:
Efficacy
The approval of sofosbuvir was based on five phase 3 trials, four of which have been published.[5] It was studied in multiple populations including interferon ineligible or intolerant. It has not been studied in a population that has failed previous protease inhibitor treatment. Sofosbuvir was studied in combination with ribavirin for genotypes 2 and 3, and in combination with pegylated interferon and ribavirin for genotypes 1, 4, 5, and 6. All sofosbuvir arms used a dose of 400 mg once daily and weight-based ribavirin.

Genotypes 2 and 3:
Four phase III trials evaluated sofosbuvir in the treatment of genotypes 2 and 3 CHC. Three of these are currently published and available for quality appraisal.[2,3] These studies included treatment-experienced patients, treatment-naïve patients, and subjects in which interferon was not a treatment option. The primary endpoint in all trials was SVR at week 12 after discontinuation of active treatment (SVR12). Across all studies, genotype 2 patients achieved consistently higher SVR rates than genotype 3 patients.

The FISSION trial was a phase 3 randomized, open-label, active control trial comparing 12 weeks of sofosbuvir plus ribavirin (n=256) to 24 weeks of peginterferon alfa-2a plus ribavirin (n=243) in genotype 2 and 3 CHC treatment-naive patients.[2] A total of 20% of patients in the sofosbuvir group and 21% in the peginterferon group had cirrhosis. Sofosbuvir plus ribavirin was shown to be noninferior to peginterferon plus ribavirin in SVR rates at week 12 (67% in both groups). Results varied based on cirrhosis or no cirrhosis and which genotype. Lowest response rates were in genotype 3 subjects with cirrhosis (34% and 30%), and highest rates were in genotype 2 patients with no cirrhosis (97% vs. 81%) for sofosbuvir treated patients and peginterferon plus ribavirin patients, respectively. Complete data for SVR24 rates are not available at this time. Relapse accounted for most treatment failures with genotype having a relapse rate of 40% compared with a 5% relapse rate in genotype 2. Subgroup analysis demonstrated that genotype 2 infection (OR 42.49, 95% CI 9.539-189.239) and an absence of cirrhosis (OR 2.935, 95% CI 1.377-6.257) were strongly associated with higher rates of SVR12. The major limitation of this study was the open-label design, increasing the risk of bias and lowering the quality of the study.

POSITRON was a phase 3 randomized, double blind trial in genotype 2 or 3 CHC patients for whom treatment with peginterferon was not an option either due to intolerance, ineligibility, or unwillingness to take interferon.[3] The most common reasons that interferon was not an option were psychiatric disorders (57%) and autoimmune disorders (19%).Patients were randomized to sofosbuvir plus ribavirin (n=207) or matching placebo (n=71) for 12 weeks. Approximately 20% of patients of patients had evidence of cirrhosis. The most common reasons for interferon ineligibility were psychiatric (58%) and autoimmune (19%), and for interferon intolerance were flue-like symptoms (32%), psychiatric (20%), thrombocytopenia (16%), and local/systemic adverse reactions (12%). Overall, 78% of subjects in the sofosbuvir group achieved SVR at week 12 compared to 0% in the placebo group ($p<0.001$). When analyzed by genotype, 93% of genotype 2

subjects and 61% of genotype 3 subjects achieved SVR in the sofosbuvir group. Likewise, 81% of patients without cirrhosis had an SVR as compared with 61% of patients with cirrhosis.

FUSION randomized blinded patients who had not had a response to prior interferon therapy to sofosbuvir plus ribavirin for 12 weeks, followed by 4 weeks of marching placebo (n=103) or 16 weeks of treatment (n=98), including 34% with compensated cirrhosis, a higher percentage than enrolled in the other phase 3 trials.[3] The rates of SVR were superior to the historical control rate of 25%, with rates of 50% in the 12-week group and 73% in the 16-week group ($p<0.001$ for both). This historical rate was agreed upon by the FDA. Patients receiving 16 weeks of treatment had a significantly higher rate of SVR than patients receiving 12 weeks of treatment (71% vs. 50%, treatment difference of -23%, 95% CI -35 to -11%, $p<0.001$). Data for SVR24 are not available at this time. Extending the treatment duration by 4 weeks increased the SVR rates in HCV genotype 3 subjects from 30% to 62%. This indicates that 12 weeks of sofosbuvir plus ribavirin is not the optimal regimen for HCV genotype 3 patients.

The VALENCE trial evaluated sofosbuvir in combination with ribavirin in genotype 2 or 3 HCV infection in treatment-naïve subjects or subjects who did not achieve SVR with prior interferon-based treatment. The original trial design was a randomized and blinded trial comparing combination therapy for 12 weeks to placebo. Based on emerging data, this trial was unblended and all genotype 2 subjects continued the original planned treatment and genotype 3 subjects were given an extended regimen of 24 weeks of sofosbuvir and ribavirin.[1] Overall SVR was 93% in genotype 2 subjects and 84% in genotype 3 subjects. This data is unpublished and therefore unable to be assessed for quality and risk of bias.

Genotypes 1,4,5,6:
NEUTRINO was a single-group, open-label poor-quality study evaluating a 12-week regimen of sofosbuvir plus peginterferon alfa-2a and ribavirin in 327 patients with treatment-naive HCV genotype 1,4,5, or 6 (89% had genotype 1, and 9% had genotype 4).[2] A total of 295 (90%) had a SVR 12 weeks after treatment. This was demonstrated to be superior to the historical response rate of 60% ($p<0.001$). Rates of SVR did not differ greatly according to HCV genotype (89% in genotype 1, 96% in genotype 4, and 100% in genotype 5/6). However, very few patients with genotype 5 or 6 were included in the trial, making it very difficult to make definitive dosing recommendations in this population. In patients without cirrhosis, 92% achieved an SVR, as compared to 80% in patients with cirrhosis. A Multivariate logistic regression showed that cirrhosis (OR 3.924, 95% CI 1.6629.265), IL28B (OR 7.989, 95% CI 1.815-35.168), and ribavirin exposure (OR 1.384, 95% CI 1.153-1.662) were all significantly associated with SVR12. Responses did not vary substantially according to race or ethnic group. The open-label, single-arm design of this trial increases the risk of bias associated with these results and the trial is therefore rated as poor quality.

Specific Populations:
Sofosbuvir has been studied in patients with HCV/HIV co-infection as well as in patients with hepatocellular carcinoma awaiting liver transplantation. Trials are currently ongoing. In patients with hepatocellular carcinoma, preliminary results with sofosbuvir has demonstrated efficacy in a limited number of subjects (pTVR12 of 64%, 23/36). Although this addresses an unmet clinical need, data is still very limited and safety is a concern as higher rates of serious adverse events, grade 3 or 4 adverse events, and deaths were reported in the pre-transplant population compared to the phase 3 trials.[5]

There have been no clinical trials in genotype 1 patients who have failed prior treatment. The FDA analysis looked at whether the high SVR rate in the treatment-naïve population provided evidence to support use of sofosbuvir in combination with peginterferon and ribavirin in patients with genotype 1 infection who are nonresponders to prior course of peginterferon and ribavirin. They predicted high SVR rates in genotype 1 peginterferon plus ribavirin treatment experienced patients. However, this is based on many assumptions.

Author: Megan Herink, Pharm.D.

The safety and efficacy of sofosbuvir was assessed in 223 HCV/HIV-1 co-infected subjects in an open-label clinical trial (PHOTON-1).[1] Subjects with genotype 1, 2, or 3 were included. All genotype 1 subjects were treatment-naïve, while patients with genotype 2 or 3 were either treatment naïve or treatment experienced. Patients were either not on antiretroviral therapy with a CD4+ cell count >500 cells/mm3 or had virologically suppressed HIV-1 with a CD4+ cell count >200 cells/mm3. Subjects received sofosbuvir and ribavirin for 12 or 24 weeks based on genotype and prior treatment history. Overall, rates of SVR were 76%, 88%, and 67% in genotype 1, 2, and 3 subjects, respectively. This data is currently unpublished and cannot be assessed for quality and risk of bias.

Safety:

The safety assessment of sofosbuvir from phase 3 data (both controlled and uncontrolled) includes subjects receiving combination therapy with sofosbuvir plus ribavirin and sofosbuvir plus ribavirin plus peginterferon alfa for time periods of 12 weeks to 24 weeks. The most common adverse events (>20%) of sofosbuvir in combination with ribavirin were fatigue and headache. The most common adverse events in combination with peginterferon alfa and ribavirin were fatigue, headache, nausea, insomnia, and anemia. The following table shows treatment-emergent adverse events reported in at least 15% of subjects in any treatment arm.

	Arm Interferon-free Regimens			**Interferon-containing Regimens**	
	PBO 12 weeks	**SOVALDI + RBV[a] 12 weeks**	**SOVALDI + RBV[a] 24 weeks**	**Peg-IFN alfa + RBV[b] 24 weeks**	**SOVALDI + Peg-IFN alfa + RBV[a] 12 weeks**
	N=71	N=650	N=250	N=243	N=327
Fatigue	24%	38%	30%	55%	59%
Headache	20%	24%	30%	44%	36%
Nausea	18%	22%	13%	29%	34%
Insomnia	4%	15%	16%	29%	25%
Pruritus	8%	11%	27%	17%	17%
Anemia	0%	10%	6%	12%	21%
Asthenia	3%	6%	21%	3%	5%
Rash	8%	8%	9%	18%	18%
Decreased Appetite	10%	6%	6%	18%	18%
Chills	1%	2%	2%	18%	17%
Influenza Like Illness	3%	3%	6%	18%	16%
Pyrexia	0%	4%	4%	14%	18%
Diarrhea	6%	9%	12%	17%	12%
Neutropenia	0%	<1%	<1%	12%	17%
Myalgia	0%	6%	9%	16%	14%
Irritability	1%	10%	10%	16%	13%

Overall, there were no significant serious adverse events. The incidence of serious adverse events was considered related to the study drug was very low (<1%) and the only serious adverse event seen in 3 or more subjects in sofosbuvir plus ribavirin group was malignant hepatic neoplasm. There were no serious or severe cardiac adverse events reported and no obvious safety issue related to cardiac toxicity. Sofosbuvir treatment was better tolerated than pegylated

Author: Megan Herink, Pharm.D.

interferon and ribavirin, with no increases in the occurrences of rash, anemia, or neutropenia. There were reported laboratory abnormalities that can be seen in the table below.

	Interferon-free Regimens			Interferon-containing Regimens	
Hematological Parameters	**PBO 12 weeks**	**SOVALDI + RBV[a] 12 weeks**	**SOVALDI + RBV[a] 24 weeks**	**Peg-IFN + RBV[b] 24 weeks**	**SOVALDI + Peg-IFN + RBV[a] 12 weeks**
	N=71	N=647	N=250	N=242	N=327
Hemoglobin (g/dL)					
< 10	0	8%	6%	14%	23%
< 8.5	0	1%	<1%	2%	2%
Neutrophils ($x10^9$/L)					
≥0.5 - < 0.75	1%	<1%	0	12%	15%
< 0.5	0	<1%	0	2%	5%
Platelets ($x10^9$/L)					
≥25 - < 50	3%	<1%	1%	7%	<1%
< 25	0	0	0	0	0

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) SVR at 24 weeks
2) Discontinuations due to adverse events
3) Mortality
4) Hepatocellular carcinoma
5) Serious Adverse events

Primary Study Endpoint:

1) SVR at 12 weeks after the end of treatment

Ref./Study Design[a]	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns

Author: Megan Herink, Pharm.D.

FISSION[2] Randomized, open-label, active-contro study, non-inferiority	1. sofosbuvir 400mg + ribavirin 12 weeks 2. Peginterferon alfa-2a plus ribavirin x 24 weeks	Treatment Naïve Genotype 2 and 3 20% with cirrhosis 87% Caucasian 3.5 black 72% genotype 3 <u>Exclusion Criteria:</u> Hepatitis B, HIV, other chronic liver disease, decompensated liver disease, psychiatric illness, pulmonary disease, cardiac disease, seizure disorder, poorly controlled diabetes, cancer, QT interval ≥ 450 ms or 500 ms if cirrhotic, major organ transplation, active substance abuse, neutrophil count <1500, Hgb < 11 in females and <12 in males, platelet ≤ 90,000 or 75,000 if cirrhotic, Creatining ≥1.5 X ULN, GFR <60, Bilirubin ≥1.5 X ULN, albumin ≤3.2	N=256 N=242	<u>SVR12:</u> 1. 67% (170/253) 2. 67% (162/243) P<0.001 for noninferiority; absolute difference of 0.3% (95% CI -7.5-8) P<0.001 <u>Genotype 2 - SVR12:</u> 1. 97% (68/70) 2. 78% (52/67) *With Cirrhosis* 1. 91% (10/11) 2. 62% (8/13 *Without Cirrhosis* 1. 98% (58/59) 2. 82% (44/54) <u>Genotype 3 - SVR12:</u> 1. 56% (102/183) 2. 63% (110/176) *With Cirrhosis* 1. 34% (13/38) 2. 30% (11/37) *Without Cirrhosis* 1. 61% (89/145) 2. 71% (99/139)	N/A – noninferiorit N/A N/A	<u>Discontinuation due to AE's:</u> 1. 1.2% (3/256) 2. 10.7% (26/242) <u>Serious AE's:</u> 1. 3% (7/256) 2. 1% (3/242)	N/A N/A	**Quality Rating:** Poor **Internal Validity: RoB** <u>Selection:</u> Randomization through centralized system. No allocation concealment as it was open-label. Patients similar at baseline; more patients in the peginterferon group had HCV RNA > 800,000 IU/ml (65% vs. 57%) <u>Performance:</u> Open-label; no blinding <u>Detection:</u> Open-label; no blinding <u>Attrition:</u> Overall attrition to week 12 post treatment visit SVR12 high at 33%; higher in the peginterferon group (22%) due to AE's and viral failure. **External Validity:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Extensive exclusion criteria; limited non-Caucasian patients whic limits the generalizability of results (only. However, 20% of patients were cirrhotic. <u>Setting:</u> 97 sites in the US, Australia, New Zealand, Italy, Sweden, and the Netherlands <u>Outcomes:</u> The primary endpoint was SVR 1 with a pre-specified 15% non-inferiority margin.

POSITRON[3] RCT, DB, PC	1. sofosbuvir 400mg + ribavirin 12 weeks 2. Placebo	Genotype 2 and 3 patient who had previously d/c'd interferon therapy due to AE's who could not take interferon therapy due to a medical condition 16% with cirrhosis Mean age 52 92% white 50% genotype 3 <u>Exclusion Criteria:</u> Pregnant, chronic liver disease, HBV, HIV, h/o malignancy, chronic immunosuppressives, drug/alcohol abuse, hepatic decompensation, excessive alcohol use, ALT/AST >10 x ULN, HB <12 for male or <11 for females, albumin <3 g/dl, bilirubin > 1.5 x ULN, CrCl <60 ml/min	N=207 N=71	<u>SVR12:</u> 1. 77.8% (161/207) 2. 0% (0/71) P<0.001 <u>Genotype 2 - SVR12:</u> 1. 92.7% (101/109) 2. 0% (0/34) *With Cirrhosis* 1. 94% (16/17) 2. 0% *Without Cirrhosis* 1. 92% (85/92) 2. 0% <u>Genotype 3 - SVR12:</u> 1. 61.2% (60/98) 2. 0% (0/37) *With Cirrhosis* 1. 21% (3/14) 2. 0% *Without Cirrhosis* 1. 68% (57/84) 2. 0%	N/A N/A N/A	<u>Discontinuation due to AE's:</u> 1. 2% (5/207) 2. 4% (3/71) <u>Serious AE's:</u> 1. 5% (11/207) 2. 3% (2/71)	NS NS	**Quality Rating: Poor** **Internal Validity: RoB** <u>Selection:</u> An interactive web response system was used to manage subject randomization and study drug assignment. Similar baseline characteristics. <u>Performance:</u> Double-dummy design <u>Detection:</u> Results blinded to the investigator and sponsor <u>Attrition:</u> The majority of patients completed assigned treatment (3.3% attrition). 17% of patients did not return for post-treatment wk 12 visit. **External Validity:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> <u>Setting:</u> 63 sites in the US, Canada, Australia, and New Zealand <u>Outcomes:</u> Data for SVR 24 not available.

FUSION[3] RCT, DB, PC, AC	1. sofosbuvir 400mg + ribavirin 12 weeks, followed by 4 weeks of matching placebo 2. Sofosbuvir 400mg + ribavirin for 16 weeks	Genotype 2 and 3in patients who did not have a response to prior treatment with interferon 34% had cirrhosis Mean age 54 86% white 63% genotype 3 30% with non-CC IL28B genotypes Exclusion Criteria: Same as above for POSITRON	N=103 N=98	SVR12: 1. 50% (50/100) 2. 73% (69/95) P<0.001 for both compared to the historical rate (25%) 1 vs. 2: Difference, -23% (95% C -35 to -11); p<0.001 Genotype 2 - SVR12: 1. 86% (31/36) 2. 94% (30/32) *With Cirrhosis* 1. 60% (6/10) 2. 78% (7/9) *Without Cirrhosis* 1. 96% (25/26) 2. 100% (23/23) Genotype 3 - SVR12: 1. 30% (19/64) 2. 62% (39/63) *With Cirrhosis* 1. 19% (5/26) 2. 61% (14/23) *Without Cirrhosis* 1. 37% (14/38) 2. 63% (25/40)	N/A N/A	Discontinuation due to AE's: 1. 1% (1/103) 2. 0 Serious AE's: 1. 5% (5/103) 2. 3% (3/98)	NS NS	**Quality Rating: Fair** **Internal Validity: RoB** Selection: Randomization through centralized system and interactive web response system. Baseline characteristics similar at baseline. Performance: Double-dummy design Detection: Results blinded to the investigator and sponsor Attrition: Low attrition to completion of treatment (1%) but Overall attrition to week 12 post treatment visit SVR12 high at 61.5%; only 50% in the 12week group returned for SVR12 **External Validity:** Recruitment: Unclear Patient Characteristics: Low number of non-white patients. High number of cirrhotic patients as well as patients with high HCV baseline levels. Setting: 67 sites in the US, Canada, New Zealand Outcomes: The primary efficacy endpoint of SVR 12 from each treatment arm were compared with a historical SVR control rate of 25%. Data for SVR 24 not available.

NEUTRINO[2] Single-group, open-label study	1. sofosbuvir plus peginterferon alfa 2a plus ribavirin x 12 weeks	Genotypes 1, 4, 5, or 6 HCV Treatment-naïve Mean age 52 4.3% > 65 years 79% white, 17% black Genotype 1 89% Genotype 4 9% Cirrhosis 17% Exclusion criteria: Prior treatment with interferon or ribavirin, HBV, HIV, chronic liver disease, decompensated liver disease, autoimmune disorders, psychiatric illness, drug or alcohol abuse, pregnancy, ALT/AST >10 x ULN, HB <12 for male or <11 for females, albumin <3 g/dl, bilirubin > 1.5 x ULN, CrCl <60 ml/min, h/o cardiac disease, severe COPD, chronic immunosuppressives, h/o malignancy	N=327	SVR12: 90% (295/327) P<0.001 (compared to historical rate of 60%) SVR12 based on genotype: GT1: 89% GT4: 96% *With cirrhosis:* 80% *Without cirrhosis:* *92%* SVR24: 92.4%	N/A	Discontinuation due to AE: 5 (2%) Serious AE's: 4 (1%)	N/A	**Quality Rating: Poor** **Internal Validity: RoB** Selection: non-randomized, open-label Performance: open-label Detection: open-label, single arm design Attrition: Low attrition to completion of treatment (2%) and low attrition to the week 12 post-treatment assessment (8%) **External Validity:** Recruitment: Unclear Patient Characteristics: Low number of non-white patients. High number of cirrhotic patients as well as patients with high HCV baseline levels. Setting: 56 sites in the US Outcomes: The primary efficacy endpoint of SVR 12 from each treatment arm were compared with a historical SVR control rate of 25%. Data for SVR 24 not available.
DB=double blinded, R=randomized, PC=placebo controlled, AC=active control, HCV=hepatitis C virus, ULN=upper normal limit, SVR=sustained virologic response, RoB=risk of bias, ARR = absolute risk reduction, NNT = number needed to treat, HBV = hepatitis B virus								

References:

1. Sofosbuvir (Sovaldi) prescribing information. Gilead Sciences: Foster City, Ca. December, 2013.

2. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013;368(20):1878–1887. doi:10.1056/NEJMoa1214853.

3. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013;368(20):1867–1877. doi:10.1056/NEJMoa1214854.

4. 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.

5. FDA Antiviral Drugs Advisory Committee Meeting. Sofosbuvir (GS-7977) Background Packate. October 25, 2013. Available at:http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/antiviraldrugsadvisorycommittee/ucm371876.pdf.

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. Yee HS, Chang MF, Pocha C, et al. Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. *Am J Gastroenterol*. 2012;107(5):669–689; quiz 690. doi:10.1038/ajg.2012.48.

8. Osinusi A, Meissner EG, Lee Y-J, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. *JAMA*. 2013;310(8):804–811. doi:10.1001/jama.2013.109309.

9. Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis*. 2013;13(5):401–408. doi:10.1016/S1473-3099(13)70033-1.

10. Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. *Lancet*. 2013;381(9883):2100–2107. doi:10.1016/S0140-6736(13)60247-0.

11. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med*. 2013;368(1):34–44. doi:10.1056/NEJMoa1208953.

12. Neupro. (rotigotine) prescribing information. Smyrna, GA; UCB, Inc; March 2012.

Author: Megan Herink, Pharm.D.

Appendix 1: Proposed PA Criteria

Sofosbuvir

Goal(s) :

- Approve treatments of chronic hepatitis C which are supported by the medical literature

Length of Authorization

- Initial trial of 12 weeks
- Continuation of therapy up to 24 weeks of total therapy based on therapy regimen and genotype

Requies PA:

- Sofosbuvir

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 or 4? Record Genotype:	**Yes:** Go to #3	**No:** Go to #4
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. Does the patient have documented HCV genotype 2 or 3? Record Genotype:	**Yes**: Go to #5	**No**: Pass to RPh, Deny For Appropriateness
5. Is the patient also being prescribed ribavirin?	**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, telaprevir, or simeprevir?	**Yes**: Pass to RPh, Deny for appropriateness	**No:** Go to #12

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12. Is the request for sofosbuvir 400 mg daily in genotype 3 (without HIV coinfection) chronic Hepatitis C?	**Yes:** Approve for 24 weeks	**No:** Go to #13 (If dose is different pass to RPh for appropriateness)
13. Is the request for sofosbuvir 400 mg daily in genotype 1, 2, or 4 chronic Hepatitis C (or genotype 3 with HIV coinfection)?	**Yes:** Approve for 12 weeks	**No:** Pass to RPh; Deny for appropriateness

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P&T Board Action: 1/30/13 (MH)
Revision(s):
Initiated:

Appendix 2: Specific Drug Information

Author: Megan Herink, Pharm.D.

PHARMACOKINETICS[12]

Parameter	Result
Oral Bioavailability	Peak concentration 0.5-2 hours post dose
Protein Binding	61-65%
Elimination	80% eliminated through the kidney
Half-Life	27 hours
Metabolism	Liver

DOSE & AVAILABILITY[12]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
400 mg	PO	Q24H	400 mg daily for 12 weeks	A dose recommendation cannot be made for severe renal impairment (CrCl <30ml/min) or ESRD/ safety and efficacy has not been established in these patients.	No dose adjustment in hepatic impairment. Safety and efficacy have not been established in patients with decompensated cirrhosis.	Safety and effectiveness has not been established	Was administered to 90 subjects aged 65 and older. Response rates were similar to that of younger subjects.	• Should be used in combination with ribavirin or in combination with pegylated interferon and ribavirin

The recommended combination therapy is as follows:

HCV Mono-infected and HCV/HIV-1 Co-infected	Treatment	Duration
Genotype 1 or 4	SOVALDI + peg-interferon alfa + ribavirin	12 weeks
Genotype 2	SOVALDI + ribavirin	12 weeks
Genotype 3	SOVALDI + ribavirin	24 weeks

*24 weeks of treatment with sofosbuvir and ribavirin can be considered for CHC patients with genotype 1 who are interferon ineligible

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* Should be used in combination with ribavirin for treatment of CHC in patients with hepatocellular carcinoma awaiting liver transplantion for up to 48 weeks or until liver transplantation

DRUG SAFETY[12]

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.

Drug Interactions:

- Drugs that are potent intestinal P-gp inducers (rifampin, St. John's wort) may alter concentrations of sofosbuvir.

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