Drug Use Research & Management Program
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Class Update with New Drug Evaluations: Hepatitis C Direct-acting Antivirals

Date of Review: September 2017
Generic Name: sofosbuvir/velpatasvir/voxilaprevir
Generic Name: glecaprevir/pibrentasvir

End Date of Literature Search: Week 1, August 2017
Brand Name (Manufacturer): Vosevi® (Gilead)
Brand Name (Manufacturer): Mavyret® (Abbvie)
Dossier Received: Yes (Mavyret), Pending (Vosevi)

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To evaluate new comparative evidence of the benefits and harms of direct-acting antivirals (DAAs) for the treatment of chronic hepatitis C (CHC) and define place in therapy for 2 new DAAs recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of CHC infection. Additionally, costs associated with the various regimens to the Oregon Medicaid program will be compared in executive session.

Research Questions:
1. Is there new comparative evidence for differences in efficacy/effectiveness or harms between available DAAs for the treatment of CHC?
2. Are there specific subpopulations based on severity of disease, extrahepatic manifestations, comorbidities, or level of fibrosis that may benefit from one particular DAA over another DAA or benefit from immediate treatment?
3. Is there new evidence to support an optimal time to initiate treatment for CHC based on improved effectiveness or less harms?
4. Is there evidence that sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX; Vosevi) or glecaprevir/pibrentasvir (G/P; Mavyret) are efficacious for the treatment of CHC and are they more effective/efficacious than other DAAs for the treatment of CHC?
5. IS SOF/VEL/VOX or G/P safer than other DAAs for the treatment of CHC?
6. Are there specific subpopulations based on severity of disease, comorbidities, or level of fibrosis that may benefit from one particular DAA over another DAA?

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Conclusions:

- There is low quality evidence from a Cochrane systematic review that DAAs reduce the risk of no sustained virologic response (SVR) (higher likelihood of achieving SVR) compared to control (54.1% vs. 23.8%; relative risk [RR] 0.44; 95% CI 0.37 to 0.52; p<0.000001, absolute risk reduction [ARR] 30.3%; number needed to treat [NNT] 4).[1] This is consistent with previous literature. There did not seem to be a difference between the different DAAs based on subgroup analysis and all subclasses of DAAs showed evidence of a significant effect on SVR. There was no difference in SVR between treatment-experienced (RR 0.50; 95% CI 0.36 to 0.69) and treatment-naïve (RR 0.48; 95% CI 0.41 to 0.56) participants.[1]
- Low-quality evidence from a Cochrane systematic review showed no difference in serious adverse events with DAAs (2.77%) compared to control (5.6%) (odds ratio [OR] 0.93; 95% CI 0.75 to 1.15; p=0.52).[1]
- Low quality evidence from a Cochrane systematic review found no difference in CHC morbidity or all-cause mortality from the DAAs compared to placebo or no intervention (OR 3.72; 95% CI 0.53 to 26.18). There were very few data on mortality with DAAs (15/2377; 0.63%) compared to control (1/617; 0.16%) from 11 trials. There was no data on hepatitis C-related morbidity.[1]
- There is insufficient evidence that treatment of CHC with any of the DAA-containing regimens improves quality of life or other clinically important outcomes including ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy or hepatocellular carcinoma (HCC).
- Limited data are available according to severity of fibrosis. Studies define patients by cirrhosis status. There is insufficient evidence from clinical trials that patients with early stages of disease (F0-F2) achieve higher SVR rates than those with more advanced disease, or whether delayed treatment leads to poorer long-term clinical outcomes. However, an assessment of the patient's readiness to treat and education on the importance of compliance and follow-up are vital for successful treatment. Factors to consider before deciding to treat early fibrosis stages (F0-F1) include: 1) the slow progression of disease to cirrhosis, and 2) possibility of superior DAA regimens in the pipeline.
- There are still several limitations in the current evidence for the treatment of CHC:
    - There is still a lack of head-to-head trials for most DAA regimens. In some populations, data on DAAs are limited to open-label, uncontrolled, or historically controlled trials.
    - Trials often exclude patients with chronic hepatitis B virus (HBV), human immunodeficiency virus (HIV), cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and severe alcohol or substance abuse. When decompensated cirrhosis is included, there are very little data in patients with Child-Pugh class C.
    - There is no direct evidence that treatment with antiviral therapy for CHC leads to improved long-term clinical outcomes in incidence of HCC, liver transplantation, or mortality. Clinical trials use SVR as the primary outcome, which remains a non-validated surrogate outcome.
    - Clinical trials do not analyze results based on Medicaid or other insurance type. However, based on age of participants, comorbidities, and nature of CHC, applicability to Medicaid patients is moderate.

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SOF/VEL/VOX NDE:

- There is low quality evidence that 8 weeks of SOF/VEL/VOX is not noninferior to 12 weeks of SOF/VEL in achieving SVR (95% vs. 98%, respectively) in patients with GT 1-6 CHC without cirrhosis or compensated cirrhosis. There is insufficient evidence that 8 weeks of SOF/VEL results in a similar SVR as 12 weeks of SOF/VEL (96%; 95% CI 91-99) in patients with GT 3 and cirrhosis but the study was not designed to directly compare SVRs between these two regimens.
- There is low quality evidence that 12 weeks of SOF/VEL/VOX achieves a SVR12 rate (96%; 95% CI 93 to 98) that is superior to a performance goal of 85% in patients with GT 1-6 without cirrhosis or compensated cirrhosis who have previously failed (relapse or virologic breakthrough) with a DAA regimen containing a NS5A inhibitor. This performance goal is arbitrary; nonetheless, the magnitude of benefit in SVR rates remains substantial.
- There is low quality evidence that 12 weeks of SOF/VEL/VOX is effective in achieving SVR12 in GTs 1-4 in those who have failed a DAA regimen not containing a NS5A inhibitor (98%; 95% CI 95 to 99). There is insufficient evidence that SOF/VEL/VOX provides a benefit over SOF/VEL for 12 weeks in achieving SVR12 in those with GT 1a (98% vs. 89%) and GT 3 (96% vs. 85%). However, the study was not designed to directly compare these regimens in these subpopulations.
- Limitations in the data evaluating SOF/VEL/VOX include:
    - Significant industry funding and conflicts of interest
    - Extensive exclusion criteria limits generalizability to the general population (renal insufficiency [CrCl < 50mL/min], psychiatric disease, significant alcohol or drug abuse in previous 12 months, significant cardiac disease, HIV, HBV, or chronic liver disease of a non-HCV etiology).
    - There were small numbers of patients with GT 3 and cirrhosis. SOF/VEL/VOX should not be used in decompensated cirrhosis.
    - There is insufficient data for SOF/VEL/VOX in patients who have failed previous therapy due to non-adherence.

G/P NDE:

- There is low quality evidence that G/P is effective and safe in the treatment of DAA-treatment experienced patients due to small numbers and poor quality trials. Data in this population comes from one published, open-label phase 2 study with a high risk of bias in GT 1 patients without cirrhosis (64% F0-F1) demonstrating an overall SVR12 rate of 92% (46/50; 95% CI 81 to 97). There was not a clear dose response, and the sample size was not large enough to determine the impact of adding RBV to therapy. Additionally, part 2 of this study compared G/P for 12 weeks (n=44) to 16 weeks (n=47) in patients with GT 1 or 4 and prior DAA treatment failure, including those with compensated cirrhosis (n=60). However, this is only available in abstract form and cannot be assessed for quality.
- Overall, there is low quality evidence that G/P is effective and safe in the treatment of DAA-treatment naïve patients with GT 1-6. G/P was approved based on four phase 3 and two phase 2 in treatment naïve patients. Only two of the trials were controlled and the others were open-label, single arm, non-randomized trials with a high risk of bias..
    - However, SVR12 rates were high in GT 1-6 with and without compensated cirrhosis. The data suggests that 8 weeks of therapy with G/P is non-inferior to 12 weeks of therapy in treatment naïve GT 1, 2, or 3 without cirrhosis. There is insufficient data to support 8 weeks of therapy in those with compensated cirrhosis. Data in GT 3 patients with compensated cirrhosis is lacking and the preferred duration remains unclear.

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- There is low quality evidence that G/P for 12 weeks results in SVR12 rates of 99% (145/146) in GT 1, 2, 4, 5 or 6 with compensated cirrhosis from an open-label trial, single arm trial with many limitations. The trial excluded those with GT 3 which is a more difficult patient population to treat.
- There is low quality evidence that G/P is safe in patients with stage 4 and 5 CKD and results in SVR 12 rates of 98% (102/104; 95% CI 95-100%) and SVR24 rates of 96% (100/104; 95% CI 95-100%).
- Limitations in the data evaluating G/P include:
    - Significant industry funding and conflicts of interest. Increased risk of reporting bias as multiple trials remain unpublished.
    - Extensive exclusion criteria limits generalizability to the general population (psychiatric disease, significant alcohol or drug abuse in previous 12 months, significant cardiac disease, HIV, HBV, or chronic liver disease of a non-HCV etiology).
    - There were small numbers of patients with GT 3 and cirrhosis. G/P should not be used in decompensated cirrhosis.
    - There is insufficient data for G/P in patients who have failed previous therapy due to non-adherence.

Recommendations:

- In accordance with the Memorandum of Understanding (MOU) between the Oregon Health Authority and Oregon Law Center:
    - Expand coverage for HCV treatment with HCV stage F-2 with no requirement to be prescribed by a specialist.
    - Expand coverage for HCV treatment for all individuals with HCV co-infected with HIV.
    - Include additional extrahepatic manifestations into coverage criteria, including diabetes with evidence of insulin resistance.
- Due to recent FDA safety alert, include baseline HBV monitoring into PA criteria (**Appendix 7**).
- Amend the PA criteria to allow for the re-treatment of HCV in those who have failed therapy with a NS5A inhibitor (**Appendix 7**) for reasons other than noncompliance.
- After evaluation of comparative costs of DAA regimens in executive session, make G/P and SOF/VEL/VOX preferred and LDV/SOF non-preferred.

Previous Conclusions:

- There is low quality evidence that the DAA regimens are effective in achieving a SVR rate of ≥ 90%. SVR rates differ between patients based on disease severity, genotype, and baseline NS5a resistant amino acid variants (RAVs). Relapse may be reduced with baseline NS5A polymorphism screening.
- The regimens that have been studied in patients with cirrhosis include mostly Child-Pugh A and B. There are very limited data in Child-Pugh C.
- From the only comparative data available, there is low quality evidence that 12 weeks SOF/VEL may be modestly superior to 12 weeks SOF + RBV in patients with GT2 (SVR 99% vs. 95%, respectively; absolute difference 5.2%; 95% CI, 0.2-10.3%; p=0.02). Treatment with 12 weeks of SOF/VEL may also be superior to 24 weeks of SOF + RBV in patients with GT3 (SVR 95% vs. 80%; respectively; absolute difference 14.8%; 95% CI 9.6-20%; p<0.001). There are no other alternative treatment regimens approved for GT2 and there is insufficient comparative data for other treatments available for GT3 (LDV/SOF + RBV or DCV/SOF).
- There are still several limitations in the current evidence for the treatment of CHC:
    - There is still insufficient evidence for the optimal treatment of patients who have had a virologic failure to a previous NS5A or NS5B inhibitor. Risk of DAA resistance is a major concern in this population.

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- There is still a lack of head-to-head trials for most DAA regimens. In some populations, data on DAAs are limited to open-label, uncontrolled, or historically controlled trials.
- Trials often exclude patients with chronic hepatitis B virus (HBV), HIV, cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and severe alcohol or substance abuse. When decompensated cirrhosis is included, there are very little data in patients with Child-Pugh class C.
- There is no direct evidence that treatment with antiviral therapy for CHC leads to improved long-term clinical outcomes in incidence of HCC, liver transplantation, or mortality.

- Given the high sensitivity and specificity of image tests to stage fibrosis (specifically, transient elastography [FibroScan], acoustic radiation force impulse imaging [ARFI], shear wave elastography [SWE]) and potential harms of liver biopsy, these less invasive options are favored for prescribers considering CHC treatment with a DAA.

Previous Recommendations:

- Continue to prioritize treatment for persons with advanced liver disease (METAVIR stage F3 or F4), as well as those at greatest risk of developing complications of liver disease, including:
  - All patients awaiting a liver transplantation
  - All patients post solid organ transplant
  - HIV coinfection with METAVIR stage F2 or greater
  - Patients with extrahepatic manifestations
- Due to extensive drug-drug interactions and safety concerns, make OMB/PTV-R + RBV and OMB/PTV-R + DAS non-preferred.
- For those with METAVIR stage F2 or lower, DAA regimens do not need to be prescribed by or in consultation with a specialist.

Background:

Chronic hepatitis C (CHC) infection is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma (HCC). It is also the leading indication for liver transplantation in the Western world.[3] The global prevalence is 1.6%, and in the United States (U.S.) approximately 50% of affected individuals remain unaware of their diagnosis.[1] The goal of treatment for CHC is to reduce the occurrence of end-stage liver disease and its related complications. However, results from clinical trials designed to evaluate long-term health outcomes or health related quality of life are not available. In addition, only about 10-20% of people with CHC go on to develop cirrhosis (8-16% of all people infected with HCV) and the time to progress to cirrhosis varies at an average of 40 years.[1] Approximately 20% of individuals infected with HCV will clear the virus. HCV is divided into seven major genotypes with variable geographical distribution and prevalence. In the U.S., GT1 infection is found in about 75% of patients with CHC; GT2 and GT3 represent about 20% of CHC patients.[3] Subgenotypes 1a and 1b are the most common subgenotypes of GT1. Cure rates for GT 1a and 1b infection may differ depending on the treatment regimen. Data suggests that fibrosis progression occurs most rapidly in patients with GT3; DAA regimens have also been less effective in patients with this genotype.[4]

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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, as measured by a sensitive polymerase chain reaction assay. It is the standard marker of successful treatment in clinical trials. There is some evidence based on only on observational data of an association of SVR and reductions in mortality, liver failure, and cancer.[3] However, the results of these observational studies should be interpreted with great caution. SVR is still a non-validated, surrogate outcome and it is not clear that SVR is a 'cure' for HCV. Many of the observational studies compared two groups that were both treated making it difficult to attribute different outcomes to treatment.[1] SVR has previously been shown as an invalid surrogate for clinical outcomes for the efficacy of interferons.[1] Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. More recent studies use SVR rate at 12 weeks (SVR12) as the primary endpoint based on evidence that the majority of patients with SVR12 maintain SVR at 24 weeks.[5]

The two major predictors of SVR are viral genotype and pre-treatment viral load.[6] Other factors associated with an increased likelihood of 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. Studies that include patients with decompensated cirrhosis, renal failure or other comorbidities, and minority racial or ethnic groups are lacking though these patients remain the most difficult to successfully treat.[7]

Patients at greatest risk for progression to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis (METAVIR stage 2 or higher). Patients with compensated cirrhosis are at risk of progressing to decompensation, developing hepatocellular carcinoma, and are at higher risk for death. Urgency to treat patients with CHC is higher when risk of decompensated cirrhosis or death from liver-related diseases is higher; treatment urgency is also higher in liver transplant recipients with CHC in order to prolong graft survival. Disease progression varies greatly among patients with compensated liver disease and the number needed to treat to prevent adverse long-term outcomes is dependent on several factors. The newer DAAs will be most beneficial in patients at highest risk for cirrhosis-related events.[8] However, treatment of CHC with DAAs at earlier stages of fibrosis incur substantial upfront costs but can be cost-effective long-term if adverse events are avoided from cure.[9] Patients with decompensated liver disease are a challenging population to treat because of symptomatic complications related to cirrhosis (i.e., jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy). Clinical trials define decompensated cirrhosis as Child-Turcotte-Pugh (CTP) class B or C cirrhosis; the majority of decompensated cirrhosis patients included in trials have CTP class B cirrhosis. Those with stage 3 to 4 disease develop end stage liver disease at a rate of 1 to 2% per year after achieving SVR.[1]

Virologic failure is defined as confirmed HCV RNA level at or above the lower limit of quantification (LLOQ) during treatment after previously being below the LLOQ; relapse is defined as confirmed HCV RNA level at or above the LLOQ after treatment after previously achieving an SVR.[10] Virologic failure is typically associated with the emergence of resistance-associated variants (RAVs) that can cause cross resistance to other DAAs in the same class.[11] Baseline RAVs exist in a minority of patients and are found in most patients who fail to achieve SVR with DAA treatment. Sofosbuvir (SOF), an NS5B inhibitor, appears to have the highest genetic barrier to resistance.[11] Genetic polymorphisms that reduce drug susceptibility have been reported for the NS5A and NS3/4A (protease inhibitor) drug classes. The presence of baseline NS5A RAVs has been reported in the range from 1% to 23% and can significantly reduce SVR12 rates in patients with GT3 treated with daclatasvir (DCV) plus SOF compared to patients without the NS5A RAV (SVR rates of 54% vs. 92%, respectively).[12] Another review of 35 clinical

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trials in patients with HCV GT1 found that pretreatment NS5A RAVs were detected in 13% of GT 1a and 18% with GT 1b and had an impact on SVR in some patients, particularly treatment-experienced patients with GT 1a HCV.[13]

Therapies to treat CHC have advanced significantly over the past several years. Prior to 2011, the combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) was the standard of care and approximately only 55-60% of patients achieved a SVR with this regimen. In 2011, the FDA approved the first generation DAAs boceprevir and telaprevir.[14] The DAAs target specific proteins of the virus, causing disruption of viral replication. There are currently four classes of DAAs, defined by their mechanism of action and therapeutic target (NS3/4A inhibitors, protease inhibitors [PIs], NS5B inhibitors and NS5A inhibitors). Due to adverse events, high rates of resistance and long duration of treatments, telaprevir was removed from the market and boceprevir is no longer a recommended therapy. Since then, a variety of second generation DAAs have been approved by the FDA resulting in many interferon-free options, fewer adverse events, and SVR12 rates that exceed 90% (Table 1). However, newer DAAs are associated with substantial cost and unknown effects on long-term clinical outcomes. A significant challenge is to identify patients who will most benefit from treatment since only 5-20% of CHC patients will develop cirrhosis over 20 years.[15] Additionally, the lack of head-to-head trials, and the use of single-arm cohort studies make it difficult to compare the relative efficacy of the different DAA regimens available. Studies do not measure long-term morbidity or mortality.

A major gap in the evidence remains the optimal treatment of patients who have had a virologic failure to a previous NS5A or NS5B inhibitor. Risk of DAA resistance is a major concern in this population. Current guidelines recommend deferral of treatment in this population, pending additional data, or if retreatment is urgent, tailoring the regimen based on resistance testing, using a treatment duration of 24 weeks and adding ribavirin (RBV).[4] Additionally, for genotype 3 (GT3) sofosbuvir (SOF) treatment-experienced patients, deferral of treatment is also recommended unless urgent retreatment is required. However, two additional pangenotypic medications have been studied in those who have failed an NS5A inhibitor. One is a triple drug combination including SOF, VEL and a new NS3/4A inhibitor, voxilaprevir (VOX).[16] The second is a combination of a NS3/4A inhibitor, glecaprevir (GLE) and a NS5A inhibitor, pibrentasvir (PIB). Glecaprevir/pibrentasvir (G/P) is approved for treatment-naïve patients with GT 1-6 for 8 weeks without cirrhosis and 12 weeks with compensated cirrhosis. It is also approved for patients who have failed treatment with a NS5A inhibitor (16 weeks) or NS3/4A protease inhibitor (12 weeks) but not both. SOF/VEL/VOX is only approved for NS5A treatment experienced patients (GT 1-6) and sofosbuvir treatment experienced for GT 1a and GT 3 (Table 1).

The Oregon Drug Use Review/Pharmacy & Therapeutics (P&T) Committee initially prioritized treatment for the fee-for-service population to patients in greatest need of treatment. Limited real-world experience and data, consideration for the number of patients waiting for treatment, limited provider expertise, and the limited number of alternative treatment options in cases of treatment resistance and patient comorbidities all played a role in prioritizing treatment. As more treatment options become available, real world experience increases, and the community standard evolves, the P&T Committee has expanded treatment in a step-wise fashion to patients with less severe disease. Current drug policies in place approve treatment for patients with fibrosis Metavir stage 3 or 4, or patients with extrahepatic manifestations at any stage of fibrosis, patients in the setting of solid organ transplant, and in patients with fibrosis Metavir stage 2 or greater coinfected with HIV. In January 2016, a Memorandum of Understanding (MOU) was signed between the Oregon Health Authority and Oregon Law Center to commit to prioritize essential health services and expand coverage for HCV to treat members with stage F2 disease by January 1, 2018, if the budgets are funded to the requested levels. Additionally, the MOU includes coverage for all HIV patients, those with fast progressing fibrosis, and extrahepatic manifestations.

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Table 1. Direct-acting Antiviral Regimens for Chronic Hepatitis C.

Drug Brand Name	Generic name	Indications	Decompensated Cirrhosis	Mechanism of Action	Duration
Daklinza® and Solvaldi®	Daclatasvir + sofosbuvir	CHC GT 1 or GT 3	GT 1, 3 with RBV	NS5A inhibitor with NS5B inhibitor	12 weeks
Epclusa®	Sofosbuvir/velpatasvir	CHC GT 1-6;	GT 1-6, with RBV	NS5B inhibitor/NS5A inhibitor	12 weeks
Harvoni®	Ledipasvir/sofosbuvir	CHC GT 1; GT 4; GT 5; GT 6	GT 1 with RBV	NS5A inhibitor/ NS5B inhibitor	8, 12, or 24 weeks
Mavyret®	Glecaprevir/pibrentasvir	CHC GT 1-6 without cirrhosis or compensated cirrhosis and GT 1 previously treated with a NS5A inhibitor or an NS3/4a protease inhibitor	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor	8-16 weeks
Olysio®	Simeprevir	CHC GT 1 in combination with sofosbuvir	Not approved	NS3/4A protease inhibitor	12 -24 weeks
Sovaldi®	Sofosbuvir	CHC GT 1; GT 2; GT 3; GT 4 Used in combination with other antivirals	Not approved	Nucleotide analog NS5B polymerase inhibitor	12 weeks
Technivie®	Ombitasvir/paritaprevir /ritonavir + ribavirin	CHC GT 4	Contraindicated	NS5A inhibitor/NS3/4A protease inhibitor	12 weeks
Viekira Pak®	Ombitasvir/paritaprevir/ritonavir + dasabuvir	CHC GT 1	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor + NS5B inhibitor	12-24 weeks
Viekira XR®	Ombitasvir/paritaprevir/ritonavir + dasabuvir	CHC GT 1	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor + NS5B inhibitor	12-24 weeks
Vosevi®	sofosbuvir/velpatasvir/voxilaprevir	CHC GT 1-6 TE with NS5A inhibitor; GT 1a or 3 TE with sofosbuvir and without an NS5A inhibitor	Contraindicated	NS5B inhibitor/NS5A inhibitor/NS3 protease inhibitor	12 weeks

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

Author: Megan Herink, Pharm.D

Date: September 2017

Zepatier®	Elbasvir / grazoprevir	CHC GT 1; GT 4	Contraindicated	NS3/4A protease inhibitor/ NS5A inhibitor	12 or 16 weeks
Abbreviations: CHC = chronic hepatitis C; GT = genotype, RBV: ribavirin; TE: treatment-experienced					

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted through week 1, August 2017. The Medline search strategy used for this review is available in **Appendix 2**, which includes search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. Randomized controlled trials and abstracts are in **Appendix 3 and 4.** Due to the evolving nature of this class and urgency to review the newly approved drugs, additional data will be evaluated as needed to meet the needs of the Oregon Health Authority.

Systematic Reviews:

Cochrane Collaboration

A systematic review and meta-analysis was conducted by the Cochrane Collaboration to assess the benefits and harms of all DAAs in the treatment of CHC.[1] The three pre-specified primary outcomes were a composite of hepatitis C-related morbidity (cirrhosis, ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy or HCC) or all-cause mortality, serious adverse events, and health-related quality of life. The proportion of participants without SVR 12 or 24 weeks after completion of treatment was a secondary outcome. A comprehensive search for RCTs comparing DAAs versus no intervention or placebo or any medication intervention except for a DAA (pegylated interferon) through October 2016 identified 138 trials including 51 different DAAs, including both discontinued DAAs and those still under development. Many trials used for FDA approval of currently available DAAs were excluded from this analysis due to wrong control or study design. Eighty five of the 138 trials assessed DAAs on the market or currently under development. All trials had a high risk of bias due to inadequate allocation concealment, unclear blinding or unblinding, incomplete outcome data or unclear selective reporting. Trials included treatment-naïve participants (95 trials), treatment-experienced participants (17), or both (24 trials). The majority of trials were in GT1 (119 trials); trials with genotypes 2-6 were extremely limited. In addition to traditional meta-analysis, Trial Sequential Analysis was performed to better control for random errors due to sparse data. HIV was an exclusion criteria in 102 trials. In all but 1 trial, the funding source was either not reported in sufficient detail or the trial was financially supported by an organization with a financial interest in the trial results.[1]

Overall, the review found very low quality evidence of no difference in CHC morbidity or all-cause mortality from the DAAs compared to placebo or no intervention (OR 3.72; 95% CI 0.53 to 26.18).[1] There were very few data on mortality with DAAs (15/2377; 0.63%) compared to control (1/617; 0.16%) from 11 trials. There was no data on hepatitis C-related morbidity. Very low-quality evidence showed no difference in serious adverse events with DAAs (2.77%) compared to control (5.6%) (OR 0.93; 95% CI 0.75 to 1.15; p=0.52). Simeprevir was the only DAA showing a significantly lower risk of serious adverse events (OR 0.62; 95% CI 0.45 to 0.86). However, when one trial with an extreme result was excluded, the meta-analysis showed no difference. There was very low quality evidence from 32 trials that DAAs reduce the risk of no SVR compared to control (17.6% vs. 69.7%, respectively; RR 0.44; 95% CI 0.37 to 0.52; p<0.000001, ARR 52.1%; NNT 2). This was confirmed by Trial Sequential Analysis and the tests for statistical heterogeneity indicated significant heterogeneity, with a high risk of bias. There did not seem to be a difference between the different DAAs based on subgroup analysis and all subclasses of DAAs showed evidence of a significant effect on no SVR. The subgroup analysis comparing the DAAs in different genotypes did show evidence of a difference between the subgroups (p=0.002; I^2 = 73.6%). There was no difference in SVR between treatment-experienced (RR 0.50; 95% CI 0.36 to 0.69) and treatment-naïve (RR 0.48; 95% CI 0.41 to 0.56) participants. There is insufficient evidence to make conclusions on quality of life. Only one trial assessed quality of life and found no difference.

None of the trials measured the effects of DAAs on clinically important outcomes including ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy or HCC.

The authors concluded that there was insufficient evidence to confirm or reject that DAAs have any clinical effects, but they do seem to reduce the risk of no SVR, which is a non-validated surrogate outcome and the clinical significance of these effects on a non-validated surrogate outcome is unclear.

Criticism from experts in this field have argued that many clinical trials on DAA therapy were excluded from this review since they did not have an untreated control group but instead used the historical control response rates. Additionally, it is unlikely to have data supporting a benefit on HCV related morbidity and all-cause mortality because of the natural history of HCV infection; clinical outcomes may take years to become apparent.[17] Furthermore, experts cite data that SVR is associated with health benefits including a decrease in liver inflammation, rate of progression of liver fibrosis, HCC, and liver transplantation.[17]

CADTH:

Three CADTH reports addressing resistance-associated variants (RAVs) in HCV treatment were identified. However, they were all Rapid Response Reports with little detail or synthesis of included studies.

1) A CADTH Rapid Response Report reviewed the comparative clinical effectiveness of NS3 or NS5B inhibitors in DAA-naïve and DAA-experienced patients with RAVs of HCV.[18] Thirteen publications met inclusion criteria and were included in the report. Many of the studies were post-hoc analyses of previously conducted studies and included only patients for whom sequencing data was available. The prevalence of baseline polymorphisms were often low and impact on outcomes is hard to determine based on this data. The included studies were limited due to small sample sizes, industry funding, and inclusion of four pooled analyses with unknown quality assessment of the included trials. The report concluded the following:

a. In GT1 HCV treatment-naïve patients, the SVR rates (92% - 100%) with SOF (n=38) and PTV +/- DAS (n=7) containing treatment regimens were comparable between patients with and without NS5B RAVs.
b. In GT1 treatment-experienced patients (prior SOF or SOF/LDV), SVR rates with SOF containing regimens (n=23) were comparable with and without NS5B RAVs (78%).
c. In HCV GT1 treatment-naïve patients, SVR rates with GZR-containing regimens were comparable between patients with and without NS3 RAVs
d. In HCV GT1 treatment-naïve patients, SVR rates with PTV or simeprevir containing regimens varied depending on the other drugs used in combination.

2) Another CADTH Rapid Response Report reviewed the clinical effectiveness of re-treatment in patients with NS5A RAVs who have failed on treatment with NS5A inhibitors.[19] Only three publications met the inclusion criteria and were included in the report. All of these were non-randomized, open-label, and non-comparative studies. One was a 'real world' study, another study reported outcomes of one single arm from an eight-arm phase 2a study, and the third study was a sub-study of ION-4. They all had a high risk of bias and were low quality. Therefore, a literature search through June 2016 did not identify data to determine if patients who fail other NS5A inhibitors could be successfully retreated using the same intervention strategies. Retreatment strategies included SOF plus SIM after failure with a DCV-based regimen, retreatment with LDV/SOF after failure with LDV/SOF, and LDV/SOF for 24 weeks after failure with 12 weeks. SVR12 was 87.5%, 91% and 89%, respectively suggesting that these regimens are effective. [19] However, the small sample sizes and low quality preclude a definitive conclusion.

3) A third CADTH Rapid Response Report reviewed the clinical effectiveness of HCV therapies containing NS5A inhibitors in DAA-naïve patients with HCV GT1 and with NS5A RAVs at baseline.[20] Current NS5A inhibitors include daclatasvir (DCV), velptasvir (VEL), ledipasvir (LDV), elbasvir (EBR), and ombitasvir (OMB). A total of 16 publications were included in the report (eight secondary analyses of RCTs, five observational, one review article and two guidelines). However, the majority of studies were with DCV + asunaprevir, which the manufacturer is no longer seeking FDA approval for. The proportion of patients with NS5A RAVs at baseline with GT 1b HCV achieved a lower SVR (38-42%) than those without (88-99%). There were limited studies identified on other treatment regimens in patients with NS5A RAVs at baseline. One study found that in patients with HCV1b treated with DCV+SMV, the proportion of patients who achieved SVR12 was 50% for patients with NS5A RAVs and 91% for those without. One study evaluated treatment with LDV/SOF and found that SVR12 was not different for those with GT1 and baseline NS5A RAVs compared to those without (99% for both groups). Lastly, a study showed a decreased SVR12 for treatment with EBR/GZR in those with RAVs (58%) compared to without (96%). There were no studies on the cost-effectiveness of screening for NS5A RAVs at baseline. There is variability in the guidelines regarding recommendations for baseline testing, and recommendations are based on low quality evidence. Due to the poor quality and limited data, definitive conclusions cannot be made.

Clinical Practice Guidelines:

The World Health Organization (WHO) updated their guidelines for the screening care and treatment of persons with CHC in April 2016.[21] The Veterans Affairs (VA) National Hepatitis C Resource Center updated treatment guidelines in March 2016,[22] and the Guidelines from the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) updated their recommendations for testing, managing, and treating CHC in April 2017.[4]

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The AASLD/IDSA guidelines are routinely updated to reflect rapidly changing evidence with the DAAs.[4] The AASLD/IDSA guideline has many limitations with poor methodological quality. The panel lacks non-specialist members and there is no assessment of risk of bias for individual studies. In addition, the authors and sponsors of the guideline have multiple conflicts of interest. The AASLD guidelines have not been updated since approval of the latest DAA regimens (SOF/VEL/VOX and G/P).

The AASLD/IDSA guidelines were updated in April 2017 with the following changes:

1. Initial Treatment of CHC:
    a. Modified the duration of LDV/SOF in patients without cirrhosis to 8 weeks for non-black, HIV-uninfected, and whose HCV RNA is less than 6 million IU/ml. Previous recommendation was 8 weeks for those without cirrhosis and whose HCV RNA is less than 6 million IU/ml. The reasoning for this change was that the analysis on duration was not randomized and baseline characteristics may have varied between 8- and 12-week groups so the guidelines no longer recommend shortening treatment duration to less than 12 weeks for HIV-infected patients and African-American patients.
        i. The original 8 week recommendation came from the ION-3 study which resulted in 8 weeks of LDV/SOF achieving non-inferiority to 12 weeks in SVR12 (94% vs. 96%). There was no significant difference based on age, sex, race, ethnicity, or GT1 subtype. Based on a post-hoc multivariate analysis conducted with the FDA, baseline viral load < 6 million IU/mL was identified as the best predictor of response. A paper by O'Brien and colleagues re-analyzed the data from ION-3 reporting missing outcome data as achieving SVR instead of treatment failures which was done in the original study.[23] The authors suggested that SVR varied by gender and IL28B genotype and found that black patients had a lower SVR rate than other racial groups (91.3% vs. 96.2%, respectively); however this association did not reach statistical significance and it is consistent with lower SVR rates seen with 12 weeks (92.6% vs. 97.2%).
    b. Updated grading of SOF/VEL for GT5 and 6
    c. Language added related to recent data regarding 8 weeks of OMB/PTV-R + DAS for GT 1b with early stage fibrosis. A single phase b, single-arm study (n=163) showed a 98% SVR with 8 weeks of OMB/PTV-R + DAS.
2. Decompensated:
    a. Recommendations (SOF/VEL or LDV/SOF) for those with decompensated cirrhosis and GT 5 or 6 were made based on an extrapolation of data from trials in patients with compensated cirrhosis and GT 5 or 6. It is unclear if these results can be generalized to those with decompensated cirrhosis and there remains very limited data with DAAs in patients with CHC GT 5 and 6 with decompensated cirrhosis. [24]

A further update from the AASLD/IDSA guidelines on treatment of adolescents with CHC is in progress.[24]

Publication of both the WHO and VA guidelines preceded the approval of SOF/VEL, SOF/VEL/VOX and G/P and these agents are only included in the AASLD/IDSA guidelines. The following recommendations are included in these guidelines:

When to Treat:

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AASLD/IDSA: Treatment for all patients regardless of disease severity is recommended, except those with short life expectancy that cannot be remediated by treatment or transplantation.[4] Little evidence exists to support initiation of treatment in patients with limited life expectancy. Prior to treatment, the guideline continues to emphasize the need to assess the patient's understanding of treatment goals and provision of education on adherence and follow-up.

WHO: HCV treatment should be considered for all persons with CHC, including persons who inject drugs. Persons with cirrhosis should be prioritized for treatment because they are at increased risk of HCC and death due to liver failure.[21]

VA: All patients with CHC who did not have medical contraindications are potential candidates for treatment. Patients with advanced liver disease are likely to derive the greatest benefit from treatment.[22] The urgency of treatment should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival in transplant recipients. In particular, patients with cirrhosis or advanced fibrosis, selected patients with HCC awaiting liver transplant, post-transplant recipients, patients with serious extra-hepatic manifestations of HCV, and women of childbearing potential who desire to conceive a child in the next 12 months should be considered for antiviral treatment in the near term. Patients with mild liver disease (METAVIR F0-2) have less urgency for treatment in the short-term, but should be informed of current treatments and the potential to cure HCV. Patients with mild liver disease (METAVIR F0-2) and no extra-hepatic manifestations can be treated in the near term if the patient desires treatment and is otherwise a candidate for HCV treatment.

Who Should Treat:
With all-oral shorter course regimens, treatment may be increasingly available outside of specialty clinics. Guidelines recommend that therapy should be managed by medical specialists with experience in the treatment of CHC infection and the physician prescribing should have knowledge of monitoring and ensuring patient adherence with therapy. The VA guideline states treatment can be provided by non-specialists trained in the management of CHC and who have access to specialists for support (Expert Opinion).[22] However, patients with decompensated cirrhosis should be seen by a specialist with experience in the management of advanced disease.

Fast Progressing:
Progression of fibrosis from stage 0 (no fibrosis) to stage 4 (cirrhosis) is variable but takes place at approximately 0.10-0.15 fibrosis units per decade.[25] The AASLD/IDSA guidelines includes the following patient populations to be at greater risk for rapidly progressive fibrosis and cirrhosis:

- HIV coinfection
- HBV coinfection and other coexistent liver disease (nonalcoholic steatohepatitis [NASH]): Several observational studies have found coinfected patients have more severe liver disease than those with monoinfection.[26] However, there are no longitudinal studies to evaluate the rate of fibrosis progression in coinfected subjects and most data comes from studies with a small sample size and retrospective design.[27] Additional studies with similar limitations have conflicting results. There are no published studies evaluating DAA regimens in patients with HBV/HCV coinfection.

Extrahepatic Manifestations:

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

The literature has linked HCV to a number of extrahepatic symptoms involving the skin, musculoskeletal, renal, cardiovascular and nervous systems.[28] There are no studies evaluating the effects of DAA-based regimens on progression of extrahepatic complications and most of the literature consists of observational studies demonstrating an association which are at risk for selection bias. The quality of the evidence for these associations is extremely variable, and it is difficult to make definitive conclusions regarding the effect of DAAs on progression of extrahepatic manifestations. The following extrahepatic manifestations have been identified:

- Cryoglobulinemia and lymphoproliferative disorder
- Dermatologic manifestations: leukocytoclastic vasculitis, porphyria cutanea tarda, lichen planus
- Insulin Resistance and Type 2 Diabetes: There is growing observational evidence that HCV increases the risk of T2DM through induction of insulin resistance and that T2DM can accelerate the course of CHC.[29]
- Lymphomas (B-cell non-Hodgkin lymphoma)

Alcohol and Drug Abuse Recommendations:
AASLD/IDSA: Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection. Persons identified as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist. For individuals with acute HCV infection who have a history of recent injection drug use, referral to an addiction medicine specialist is recommended when appropriate.[4]

WHO: An alcohol intake assessment is recommended for all persons with HCV infection followed by the offer of a behavioral alcohol reduction intervention for persons with moderate-to-high alcohol intake. Persons who inject drugs should be assessed for antiviral treatment. Persons who inject drugs are at increased risk of HCV-related disease and transmission, as well as for all-cause morbidity and mortality, and therefore require specialized care and should be considered as a priority for HCV treatment.[21]

VA: All patients should be evaluated for current alcohol and other substance use, with validated screening instruments such as AUDIT-C (www.hepatitis.va.gov/provider/tools/audit-c.asp).[22] Patients with a history of substance or alcohol use disorders should be considered for HCV antiviral therapy on a case-by-case basis. There are no published data supporting a minimum length of abstinence as an inclusion criterion for HCV antiviral treatment, while multiple studies show successful treatment of patients who have short durations of abstinence or infrequent use of alcohol. Thus, automatic disqualification of patients as treatment candidates based on length of abstinence is unwarranted and strongly discouraged. The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once a month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. Patients with active substance or alcohol use disorders may be considered for therapy on a case-by-case basis, and care should be coordinated with substance use treatment specialists.[22]

Testing for Liver Cirrhosis:

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AASLD/IDSA: The use of biopsy, imaging, and/or noninvasive markers appropriate to evaluate advanced fibrosis should be considered in HCV patients planning on treatment (Class I, Level A). [4] Guidelines also recommend that a biopsy should be considered for any patient with discordant results between 2 modalities that would affect clinical decision making. If direct biomarkers or elastography are not available, the AST-to-platelet ratio index (APRI) or FIB-4 index score can help, although neither test is sensitive enough to rule out significant fibrosis.

WHO: In resource-limited settings, it is suggested that the APRI or FIB-4 test be used for the assessment of hepatic fibrosis rather than other noninvasive tests that require more resources such as elastography or FibroTest (Conditional recommendation, low quality of evidence).[21] FibroScan, which is more accurate than APRI and FIB-4, may be preferable in settings where the equipment is available and the cost of the test is not a barrier to testing.[21]

VA: Testing recommendations include clinical findings (low platelet count), abdominal imaging for features of portal hypertension, liver fibrosis imaging (FibroScan and Acoustic Radiation force impulse [ARFI]), serum markers of fibrosis (APRI, FIB-4, FibroSure, FibroTest), and liver biopsy as options. Liver biopsy should be reserved for situations in which the risks and limitations of the procedure are outweighed by the benefits of obtaining information via this technique.[22]

Decompensated Cirrhosis:
All guidelines recommend patients with decompensated cirrhosis be considered for treatment on a case by case basis and should involve an experienced specialist who is able to manage complications.

Recommendations for performing pre-treatment resistant testing:
The VA guidelines recommend that NS5A resistance-associated variants (RAV) testing should be performed at baseline prior to initial treatment for GT 1a-infected patients who are being treated with EBR/GZR and for GT3 patients who are being treated with DCV.[22] Patients who fail DAA treatment usually have RAVs to one or more classes of DAAs and should have testing done for each of the drug classes before being considered for re-treatment.

Retreatment:
The AASLD/IDSA guidelines have retreatment recommendations for those who have failed treatment with PEG/RBV or PEG/RBV + a NS3 PI (telaprevir, boceprevir, or simeprevir) that are similar to initial treatment recommendations for GT1 (Table 2). For those who have failed sofosbuvir plus RBV, LDV/SOF is the recommended therapy for GT1 based on limited data. For NS5A treatment-experienced patients, the guidelines recommend the newer agents, SOF/VEL/VOX or G/P with a higher strength of recommendation for SOF/VEL/VOX.. [24]

Recommended Treatment Options:
Treatment options based on genotype and treatment history are included in the following table:

Table 2: Guideline Recommended Treatment Options

GT	Treatment History	Cirrhosis Status	Veterans Affairs Guidelines[22]	AASLD/IDSA Guidelines[4]	WHO Guidelines[21]

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1	***Naïve or Experienced (PEG-INF/RBV only)***	***Non-cirrhotic***	EBR/GZR x 12 weeks ** LDV/SOF x 12 weeks	EBR/GZR x 12 weeks** LDV/SOF x 8-12 weeks SOF/VEL x 12 weeks G/P x 8 weeks	DCV/SOF x 12 weeks LDV/SOF x 8-12 weeks
1		***Cirrhotic***	LDV/SOF + RBV x 8-12 weeks	EBR/GZR x 12 weeks** LDV/SOF x 12 weeks SOF/VEL x 12 weeks G/P x 12 weeks	DCV/SOF +/- RBV x 12 weeks LDV/SOF +/- RBV x 12 weeks
1		***Decompensated Cirrhosis***	LDV/SOF + RBV x 12 weeks	LDV/SOF + RBV x 12 week SOF/VEL + RBV x 12 week DCV/SOF + RBV x 12 week	DCV/SOF x 12 weeks
1	***Experienced (prior sofosbuvir)***	***Non-cirrhotic or compensated cirrhosis***	EBR/GZR x 12 weeks +/- RBV	SOF/VOL x 12 weeks (GT 1 b) G/P x 12 weeks SOF/VEL/VOX x 12 weeks (GT 1a)	
1	***Experienced (Prior NS3A/4A inhibitor)***	***Non-cirrhotic or compensated cirrhosis***	EBR/GZR + RBV x 12 weeks	LDV/SOF X 12 weeks SOF/VEL x 12 weeks G/P x 12 weeks	N/A
1	***Experienced (prior NS5A-containing regimen)***	***Non-cirrhotic or compensated cirrhosis***	Test for RAPs to NS5A prior to re-treatment. Consult with an expert based on results.	SOF/VEL/VOX x 12 weeks	N/A
2	***Naïve***	***Non-cirrhotic***	SOF + RBV x 12 weeks	SOF/VEL x 12 weeks G/P x 8 weeks	SOF + RBV X 12 weeks
2		***Cirrhotic***	SOF + RBV x 16 weeks	SOF/VEL x 12 weeks G/P x 12 weeks	SOF + RBV x 16 weeks
2		***Decompensated***	SOF + RBV x 16 weeks	SOF/VEL + RBV x 12 weeks DCV/SOF + RBV x 12 weeks	SOF + RBV x 16 weeks
2	***Experienced (prior PEG-IFN/RBV)***	***Non-cirrhotic or Compensated Cirrhotic***	SOF + RBV x 16 weeks	SOF/VEL x 12 weeks G/P x 8-12 weeks	N/A
2	***Experienced (SOF + RBV)***	***Non-cirrhotic or Compensated Cirrhotic***	The optimal DAA-based therapy for this patient population is not known. Consult with an expert	SOF/VEL x 12 weeks G/P x 12 weeks	N/A
3	***Naïve***	***Non-cirrhotic***	LDV/SOF + RBV x 12 weeks*	G/P x 8 weeks SOF/VEL X 12 weeks	DCV/SOF X 12 weeks
3		***Compensated Cirrhotic***	DCV/SOF + RBV x 12 weeks	SOF/VEL x 12 weeks G/P x 12 weeks	DCV/SOF + RBV x 12 weeks
3		***Decompensated Cirrhosis***	DCV/SOF + RBV x 12-24 weeks	SOF/VEL + RBV x 12 weeks DCV/SOF + RBV x 12 weeks	N/A
3	***Experienced (prior PEG-IFN/RBV only)***	***Non-cirrhotic***	LDV/SOF + RBV X 12 weeks*	SOF/VEL x 12 weeks	N/A
3		***Compensated Cirrhotic***	DCV/SOF + RBV X 12 weeks- 24 weeks	SOF/VEL/VOX x 12 weeks EBV/GZR + SOF x 12 weeks	DCV/SOF + RBV x 24 weeks
3	***Experienced (NS5A or SOF)***	***Non-cirrhotic or Compensated Cirrhotic***	The optimal therapy for this patient population is based on expert opinion andNS5A resistance testing.	SOF/VEL/VOX x 12 weeks	N/A
4	***Naïve***	***Non-cirrhotic***	EBV/GZR x 12 weeks LDV/SOF x 12 weeks	SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	DCV/SOF x 12 weeks LDV/SOF x 12 weeks

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				G/P x 8 weeks	
4		***Compensated Cirrhotic***	EBV/GZR x 12 weeks LDV/SOF x 12 weeks	SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks G/P x 12 weeks	DCV/SOF x 24 weeks DCV/SOF + RBV x 12 weeks LDV/SOF x 24 weeks LDV/SOF + RBV x 12 weeks
4		***Decompensated Cirrhosis***	N/A	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 week DCV/SOF + RBV X 12 week	N/A
4	***Experienced (prior PEG-IFN/RBV only)***	***Non-cirrhotic or Compensated Cirrhotic***	OMB/PTV-R + RBV x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks G/P x 8 -12 weeks	N/A
	Experienced (NS5A or SOF)	***Non-cirrhotic or compensated cirrhotic***	N/A	SOF/VEL/VOX x 12 weeks	N/A
5/6	***Naïve or Experienced (prior PEG-IFN/RBV only)***	***Non-cirrhotic or Compensated Cirrhotic***	N/A	SOF/VEL x 12 weeks LDV/SOF x 12 weeks G/P x 8-12 weeks	LDV/SOF X 12 weeks
5/6	***Experienced (NS5A or SOF)***	***Non cirrhotic or Compensated Cirrhotic***	N/A	SOF/VEL/VOX x 12 weeks	N/A

**No baseline NS5A RAVs. Abbreviations: CTP = Child-Turcotte-Pugh; DAA = direct acting antiviral; DCV = daclatasvir; EBV/GZR = elbasvir/grazoprevir; G/P = glecaprevir/pibrentasvir, LDV/SOF = ledipasvir/sofosbuvir; OMB/PTV-R + DAS = ombitasvir, paritaprevir and ritonavir with dasabuvir; PEG-IFN = pegylated interferon; VEL/SOF = velpatasvir/sofosbuvir; RAP = resistance-associated polymorphisms; RAV = resistance-associated variant; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SOF/VEL/VOX = sofosbuvir, velpatasvir, voxilaprevir

National Institute for Health and Care Excellence (NICE)

A technology appraisal guidance was published in January 2017 regarding SOF/VEL for treating CHC.[30] NICE recommended SOF/VEL as an option for treating CHC in adults, only if the company provides the drug with the agreed upon discount. It was recommended for HCV GT 1-6 with or without compensated cirrhosis as well as for those with decompensated cirrhosis (with ribavirin), except for untreated GT2 without cirrhosis. This recommendation was based on review of the four key randomized controlled phase III trials evaluating SOF/VEL on SVR. The committee concluded that the trials showed high SVRs (89% to 100%) regardless of HCV genotype, cirrhosis stage or treatment history. However, there was a high risk of bias in the open-label trials. The committee also concluded that the adverse events associated with SOF/VEL are generally tolerable. Additionally, they concluded there is insufficient evidence to consider those with drug-resistant mutations separately to the overall population.[30]

New FDA Safety Alerts:

In October 2016, the FDA warned about the risk of hepatitis B virus (HBV) reactivation in any patient with a current or previous infection with HBV undergoing treatment with DAAs.[31] This HBV reactivation can result in serious liver problems or death. Twenty four cases of HBV reactivation while receiving DAAs were found in the literature. HBV occurred an average of 52 days (range of 4-8 weeks) after starting treatment. Three patients progressed to decompensated liver disease and 2 of the patients died. The mechanism of HBV reactivation is not known.[31] Since patients with HBV co-infection were excluded from all phase III trials of DAAs, HBV reactivation was not identified in clinical trials.

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The FDA recommends that all patients should be screened for evidence of current or prior HBV infection prior to starting treatment with DAAs; monitor is recommended for HBV reactivation during treatment and following treatment.[31] Clinical guidelines were updated to recommend that all patients be tested for HBsAG, HBsAb, and HBcAb status.[32] In patients with serologic evidence of HBV, baseline HBV DNA should be measured prior to DAA treatment and monitored during therapy and for several weeks after.[31] Antiviral therapy for HBV infection should be given if criteria for treatment are met.

New Indications:
In April 2017, the FDA approved SOF (Sovaldi) and LDV/SOF (Harvoni) to treat HCV in children ages 12 to 17 weighing at least 35 kilograms.[33] These are the only two DAAs approved for children with HCV. It is estimated that there are 23,000 to 46,000 children in the U.S. with HCV.[34]

Sofosbuvir was approved in combination with ribavirin for those with GT 2 or 3 without cirrhosis or with compensated cirrhosis based on an ongoing unpublished, open-label study in 13 adolescents with GT2 (12 weeks) and 37 adolescents with GT3 (24 weeks).[35] Results are not available on clinicaltrials.gov. According to the FDA, 100% of patients with GT2 and 97% of patients with GT3 achieved SVR12.

SOF/LDV was approved for HCV GT 1, 4, 5 or 6 without cirrhosis or mild cirrhosis based on an ongoing, unpublished and open-label study (n=100). Results are not available on clinicaltrials.gov.[36] According to the FDA, 98% of patients achieved SVR12.

Children with GT 1 or 4 are currently being studied in a trial of OMB/PTV-R +/- DAS.

An update from the AASLD/IDSA guidelines regarding treatment of CHC in adolescent patients is in process.

NEW DRUG EVALUATIONS:

Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX)

SOF/VEL/VOX is approved for 1) genotype 1, 2, 3, 4, 5 or 6 CHC in those who have previously been treated with an HCV regimen containing an NS5A inhibitor and 2) genotype 1a or 3 infection in those who have previously been treated with an HCV regimen containing SOF without an NS5A inhibitor.[16] See **Appendix 5** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

SOF/VEL/VOX was studied four phase 3 studies (Table 3) in both DAA treatment naïve and DAA-treatment experienced patients.[2,37] Since VOX is a protease inhibitor, those with decompensated cirrhosis are not eligible for treatment and were excluded from all clinical trials. Only those with Child-Pugh A compensated cirrhosis were included.

Table 3: Summary of Phase 3 Clinical Trials of SOF/VEL/VOX

	DAA-Treatment Experienced		DAA-Treatment Naïve	
	POLARIS-1	POLARIS-4	POLARIS-2	POLARIS-3
Genotypes included	1, 2, 3, 4, 5, 6	1, 2, 3, 4	1, 2, 3, 4, 5, 6	3
Cirrhosis Inclusion	Non-cirrhosis or compensated cirrhosis	Non-cirrhosis or compensated cirrhosis	Non-cirrhosis or compensated cirrhosis	Cirrhosis only
Duration of SOF/VEL/VOX	12 weeks	12 weeks	8 weeks	8 weeks

DAA-Treatment Naive

POLARIS 2 (n=943) and 3 (n=220) are 2 open-label trials in DAA-treatment naïve patients that compared SOF/VEL/VOX for 8 weeks of therapy to SOF/VEL for 12 weeks. POLARIS 2 included those with GT 1-6 either without cirrhosis or compensated cirrhosis (~18%) and POLARIS 3 included patients with GT 3 and cirrhosis only. In the POLARIS-2 trial, the SVR rate was 95% (95% CI 93 to 97) for those receiving 8 weeks of SOF/VEL/VOX and 98% (95% CI 96-99) among those receiving 12 weeks of SOF/VEL. The 8 week therapy did not meet the pre-specified criteria for noninferiority to 12 weeks of SOF/VEL. There was a higher rate of relapse among patients with GT1a (n=14) who received 8 weeks of SOF/VEL/VOX compared to 1 patient in the SOF/VEL group. Overall, the SVR rates were 94% in those who had baseline RAVs but was only 89% among those with baseline RAV with HCV GT 1a. Among patients with cirrhosis, 91% (82/90) of patients receiving SOF/VEL/VOX had SVR, as compared with 99% (83/84) of patients receiving SOF/VEL. In POLARIS-3, the SVR rate was 96% (95% CI 91-99) in both the SOF/VEL/VOX for 8 week group and the SOF/VEL for 12 week group in GT3 patients with cirrhosis. There were very few discontinuations due to adverse events. There were more slightly more adverse events in the SOF/VEL/VOX group compared to SOF/VEL including diarrhea and nausea due to the presence of a protease inhibitor. All patients with baseline RAVs achieved a SVR. Major limitations of these trials include its open-label design, exclusion criteria including HBV, HIV, decompensated cirrhosis, few non-white patients or those with genotypes 4, 5, and 6, industry funding and conflicts of interest, and lack of long term clinical outcomes. SOF/VEL/VOX currently does not have FDA approval for treatment-naïve patients and would not be an ideal choice of therapy since it was not found to have a significant benefit over SOF/VEL and there are currently no treatment options available for those who fail therapy with SOF/VEL/VOX. Therefore, these trials are not included in the evidence table below.

DAA-Treatment Experienced

Approval of SOF/VEL/VOX for treatment-experienced subjects was approved based on two phase 3 trials in patients who had been previously treated with a DAA-containing regimen.[2] POLARIS-1 was in GT 1-6 infection in those who had previously received a regimen with a NS5A inhibitor and POLARIS-4 was in those who had previously received a DAA but not an NS5A inhibitor. Both trials excluded patients with decompensated cirrhosis.

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POLARIS-1 was double-blinded to investigators and patients for those with GT 1 only.[2] Patients were randomized to SOF/VEL/VOX for 12 weeks or placebo. Although the trial included GTs 1-6, only those with GT 1 were randomized to a deferred treatment, placebo group and there were limited numbers of patients with other GTs (5 with GT 2, 78 with GT 3, 22 with GT 4, and 7 with GT 5 or 6). This was lower than what was expected to be enrolled based on the study protocol. The study originally required 450 patients in Group 1 to achieve 90% power, but only 262 patients were ultimately included in this arm. This was decreased to 280 in the amended protocol to achieve 90% power with no further information. The primary outcome was SVR at 12 weeks post treatment. Over half of the subjects had been previously treated with a NS5A inhibitor (LDV, DCV, or OMB) plus NS5B inhibitor (SOF), while the remainder had the addition of a NS3 inhibitor. In the primary efficacy analysis, the SVR12 was compared to a performance goal of 85%. The basis for this performance goal was the overall trend toward increasing SVR rates; however, this is lower than trials have been demonstrating with currently recommended regimens. Approximately 46% (n=121) in the SOF/VEL/VOX group and 51% (n=34) in the placebo group had compensated cirrhosis. Eighty three percent of subjects had RAVs at baseline, the majority with an NS5A RAV. Overall, the SVR rate was 96% (95% CI 93 to 98), which was found to be superior to the pre-specified 85% performance goal, as expected ($p<0.001$). Although not statistically different, the SVR rate was slightly lower at 93% (113/121) in those with cirrhosis compared to 99% (140/142) in those without.[2] Of the 253 patients with a SVR12, 249 returned for a SVR24 and all patients had a SVR. Only 6 patients had a relapse, and only one had a virologic breakthrough, despite the high number of subjects with baseline RAV (83%). Baseline resistance did not seem to have an impact on SVR rates.

POLARIS-4 was an open-label trial with similar inclusion and exclusion criteria except that this trial did include patients previously treated with a regimen that did not contain a NS5A inhibitor. [2] Those whose only DAA exposure was an NS3/4A protease inhibitor were excluded. Patients were assigned to receive either SOF/VEL/VOX or SOF/VEL for 12 weeks; however, the study was not powered for a comparison between SOF/VEL/VOX and SOF/VEL. The majority of subjects in POLARIS-4 also were GT 1 (144/333). There were no patients with GT 5 or 6 enrolled. The majority of patients (85%) had previously received therapy with SOF. The overall SVR12 rate was 98% (95% CI 95 to 99) with SOF/VEL/VOX which was superior to the performance goal of 85%. The SVR12 with SOF/VEL was 90% which was not statistically superior to the performance goal ($p=0.09$). The SVR12 rate according to HCV genotype is included in Table 4. Although the regimens were not directly compared, there was a numerical benefit in SVR12 with SOF/VEL/VOX compared to SOF/VEL in those with GT 1a (98% vs. 89%) and GT 3 (96% vs. 85%). As there was no noticeable benefit in other genotypes and SOF/VEL is a reasonable treatment option, SOF/VEL/VOX is not FDA approved for these other genotypes. Nonetheless, SOF/VEL/VOX appears effective in achieving SVR 12 in GTs 1-4 in those who have failed a DAA-regimen not containing a NS5A inhibitor. The current AASLD guidelines recommend treatment with LDV/SOF in these populations based on 2 small trials.[38,39] Only 1 subject in the SOF/VEL/VOX group had a virologic relapse and 14 in the SOF/VEL group experienced virologic relapse after treatment. Of these patients, 8 had GT3 and 5 had GT1a.

Table 4: SVR12 rates with SOF/VEL/VOX in DAA-treatment experienced patients

	POLARIS-1	**POLARIS-4**	
		SOF/VEL/VOX	***SOF/VEL***
Overall	96% (253/263)	98% (178/182)	90% (136/151)
Compensated Cirrhosis	99% (140/141)	98% (82/84)	86% (59/69)

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Without Cirrhosis	94% (113/121)	98% (96/98)	94% (77/82)
GT 1a	96% (97/101)	**98% (53/54)**	**89% (39/44)**
GT 1b	100% (45/45)	96% (23/24)	95% (21/22)
GT 2	100% (5/5)	100% (31/31)	97% (32/33)
GT 3	95% (74/78)	**96% (52/54)**	**85% (44/52)**
GT 4	91% (20/22)	100% (19/19)	NA
GT 5	100% (1/1)	NA	NA
GT 6	100% (6/6)	NA	NA

Trial Limitations:

Both trials were funded by Gilead. Extensive exclusion criteria in both trials (renal insufficiency [CrCl <50 mL/min], psychiatric disease, significant alcohol or drug abuse in the previous 12 months, significant cardiac disease, HIV, HBV, and chronic liver disease of a non-HCV etiology) limits generalizability to the general population with multiple medical comorbidities. Due to drug-drug interactions, statins, proton-pump inhibitors, amiodarone, and strong CYP3A4 inhibitors were not allowed in the study. Additionally, there were small numbers of patients with GT3 and cirrhosis as well as other rare genotypes. There were limited patients who had been previously treated with VEL or ELB.

According to the study protocol, health related quality of life was measured using the SF-36, Chronic Liver Disease Questionnaire, Fatigue Index, and Work Productivity and Activity Impairment Questionnaire. However, results for these outcomes were not reported in the study.

The relevance of using a performance goal comparator in both trials is unclear. A goal of 85% was chosen; however, this is lower than what is expected with regimens approved today. POLARIS-4 was open-label in its entirety, and POLARIS-1 was open-label to treatment assignments for all genotypes except GT 1. This increases the risk of selection, performance and detection bias. Lastly, FDA approval for SOF/VEL/VOX for patients who are treatment experienced with a non-NS5A DAA regimen included only GT 1a and GT 3 based on subgroup analyses from the study. However, the study wasn't designed to detect differences between genotype subtypes.

Clinical Safety:

Overall, approximately 75% of subjects experienced an adverse event. Most common adverse events included headache, fatigue, diarrhea and nausea (Table 5). However, these were mild in nature, and there were very few (<5) discontinuations due to adverse events overall. Similarly, there were very few serious adverse events. There did not appear to be more elevations in liver enzymes in the SOF/VEL/VOX group compared to placebo.

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Table 5: Common Adverse Events from Clinical Trials

	POLARIS-1		POLARIS-4	
	SOF/VEL/VOX	Placebo	SOF/VEL/VOX	SOF/VEL
Headache	21%	14%	23%	23%
Fatigue	17%	15%	19%	23%
Diarrhea	13%	9%	14%	3%
Nausea	13%	7%	10%	3%

There are potential drug-drug interactions that need to be accounted for with SOF/VEL/VOX since they are substrates of P-glycoprotein and CYPP450 enzymes. Treatment with SOF/VEL/VOX is not recommended for those with moderate or severe hepatic impairment (Child-Pugh B or C) due to a presumed class effect of the protease inhibitors and the increased risk of serious liver injury in those with underlying advanced liver disease.

Table 6. Pharmacology and Pharmacokinetic Properties.

Parameter	Sofosbuvir	Velpatasvir	Voxilaprevir
Mechanism of Action	NS5B RNA inhibitor	NS5A protein inhibitor	V NS3/4a protease inhibitor
Oral Bioavailability	NA	NA	NA
Distribution and Protein Binding	61% to 65%	>99%	>99%
Elimination	Urine (80%); feces (14%)	94% in feces	94% in feces
Half-Life	0.4 hours	17 hours	33 hours
Metabolism	Hepatic (non-CYP mediated)	Hepatic (CYP2B6, CYP2C8, CYP3A4)	Hepatic (CYP3A4)

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Date: September 2017

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Hepatocellular Carcinoma
2) Mortality
3) Liver Transplant
4) Decompensated Liver Disease
5) Discontinuation Rates Due to Adverse Events
6) Severe Adverse Events
6) Quality of Life

Primary Study Endpoint:

1) Sustained Virologic Response at 12 weeks post treatment (SVR12)

Table 7. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1.Bourliere et al. (Polaris-1)[2] phase 3 trial RCT, DB, PC, MC	1. SOF/VEL/VOX 2. Placebo (GT1 only) (Deferred treatment) X 12 weeks	Demographics: GT1-6, DAA-experienced chronic HCV with an NS5A inhibitor Key Inclusion Criteria: >18 y/o, previous tx duration ≥4 weeks, GT1: previous NS5A inhibitor or 2 DAAs from different classes, other GT: previous DAA regimen Key Exclusion Criteria: noncompliance to previous regimens, decompensated cirrhosis, unstable	ITT: 1. 264 2. 152 FAS: 1. 263 2. 152 Attrition: 1. 3 2. 3	SVR12: 1. 253/263; 96% (95% CI 93 to 98) P<0.001 for superiority compared to 85% performance goal SVR24: 1. 249/263; 95% (CI not reported)	N/A	Discontinuations due to adverse events: 1. 1 (<1%) 2. 3 (<1%)	NS	**Risk of Bias (low/high/unclear)**: Selection Bias: low; interactive web response system used for randomization and treatment concealment. Only GT1 patients were randomized to placebo. Performance Bias: unclear; adequate blinding of participants and investigators, double-dummy design used. Only those with GT1 were blinded. Detection Bias: unclear; unclear if outcome assessors were blinded. Attrition Bias: low; FAS (all randomized pts who took ≥ 1 dose of drug). Missing data for HCV RNA imputed from last study dose. SVR24 data imputed as SVR12 if missing. Very low attrition overall. Reporting Bias: unclear; health related quality of life was listed as an exploratory outcome but was not reported in results. Also SVR results of deferred treatment group unknown. **Applicability**:

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		psychiatric disease, significant cardiac disease, malignancy, abnormal AST/ALT, bilirubin >1.5 ULN, plts <50,000, HgA1C >8.5%, CrCl <50mL/min, Hg <10, albumin <3, chronic liver disease of non-HCV origin, HBV, HIV, alcohol or drug abuse within the previous 12 months, medications (amiodarone, PPIs, statins, or anticonvulsants)						Patient: Majority (300/415) were GT1. GT2: 5, GT3: 78, GT4:22, GT5:1. 46% had cirrhosis, 80% white. 85% of subjects failed previous treatment due to relapse. 133/263 had failed previous treatment with LDV. Intervention: No concerns. The addition of a protease inhibitor limits treatment to those without cirrhosis or Child-Pugh class A only. Comparator: Compared to a performance goal of 85%. This is lower than expected SVR12 with study drug. Outcomes: SVR12 remains an invalidated surrogate outcome. No evidence on long-term clinical outcomes. Setting: Multicenter: US, Canada, New Zealand, Australia. France, Germany, U.K. Sponsored by Gilead. Gilead was involved in data collection, statistical analysis, and writing of the manuscript.
2. Bourliere et al. (Polaris-4)[2] Open-label, RCT, MC	1. SOF/VEL/VOX 2. SOF/VEL x 12 weeks	Demographics: GT1, 2, or 3,DAA-experienced chronic HCV without an NS5A inhibitor Key Inclusion Criteria: >18 y/o, previous tx duration ≥4 weeks, GT1: previous NS5A inhibitor or 2 DAAs from different classes, other GT: previous DAA regimen	ITT: 1. 182 2. 151 FAS: 1. 182 2. 151 Attrition: 1. 0 2.2	SVR12: 1. 178/182; 98% (95% CI 95 to 99)* *P< 0.001 for superiority compared to 85% performance goal 2. 136/151; 90% (95% CI 84 to 94)** **p=0.09 compared to 85% performance goal	N/A	Discontinuations due to adverse events: 1. 0 2. 1 (<1%)	NS	**Risk of Bias (low/high/unclear)**: Selection Bias: high; open-label. Randomization via an interactive web response system. Performance Bias: high; open-label Detection Bias: high; open-label Attrition Bias: low; FAS (all randomized pts who took ≥ 1 dose of drug). Missing data for HCV RNA imputed from last study dose. SVR24 data imputed as SVR12 if missing. Very low attrition overall. Reporting Bias: unclear; health related quality of life was listed as an exploratory outcome but was not reported in results. **Applicability**: Patient: Majority (144/333) were GT1. GT2: 64, GT3: 106, GT4:19. 85% received previous

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		Key Exclusion Criteria: noncompliance to previous regimens, decompensated cirrhosis, unstable psychiatric disease, significant cardiac disease, malignancy, abnormal AST/ALT, bilirubin > 1.5 ULN, plts < 50,000, HgA1C > 8.5%, CrCl < 50mL/min, Hg < 10, albumin < 3, chronic liver disease of non-HCV origin, HBV, HIV, alcohol or drug abuse within previous 12 months, medications (amiodarone, PPIs, statins, or anticonvulsants)						therapy with SOF. 88% were white, 46% with cirrhosis. Intervention: No concerns. The addition of a protease inhibitor limits treatment to those without cirrhosis or Child-Pugh class A only. Comparator: Compared to a performance goal of 85%. This is lower than expected SVR12 with study drug. Outcomes: SVR12 remains an invalidated surrogate outcome. No evidence on long term clinical outcomes. Setting: Multicenter: U.S., Canada, New Zealand, Australia, France, Germany, U.K Sponsored by Gilead. Gilead was involved in data collection, statistical analysis, and writing of the manuscript.

Abbreviations: AE = adverse events; ALT = alanine aminotransferase; ; ARI = absolute risk increase; ARR = absolute risk reduction; CI = confidence interval; CKD = chronic kidney disease; CrCl = creatinine clearance; CV = cardiovascular; DB = double-blind; DAA = direct acting antiviral; D/C = discontinue; DM = diabetes mellitus; DTG = deferred treatment group; EBR = elbasvir; EF = ejection fraction; FAS = full analysis set; FDA = U.S. Food and Drug Administration; GT = genotype;; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; h/o = history of; HG = hemoglobin; MC = multi-centered; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; OR = odds ratio; PC = placebo-controlled; PBO = placebo;; PG = parallel group; PP = per protocol; PT=prothrombin time; RBV = ribavirin; RCT = randomized controlled trial; RR = relative risk; RRR = relative risk reduction; SAE = serious adverse event; SE = standard error; SVR12 = sustained virologic response at 12 weeks after therapy completed; TE = treatment experienced; TN = treatment naïve; Tx = treatment; ULN = upper limit of normal; wk = weeks; wt = weight; y = years; µL = microliters.

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Glecaprevir/Pibrentasvir (G/P)

G/P is FDA approved for 1) Treatment naïve patients with GTs 1-6 for 8 weeks without cirrhosis or 12 weeks with compensated cirrhosis and 2) GT 1 prior treatment with an NS5A inhibitor without an NS4/4A protease inhibitor for 16 weeks and 3) GT 1 prior treatment with an NS3/4A protease inhibitor but not an NS5A inhibitor for 12 weeks, and 4) Prior treatment with PEG/RBV or SOF for 8-16 weeks. **Appendix 6** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

The FDA approved G/P based on evidence from nine clinical trials (n=2369) in both treatment naïve and treatment experienced patients without cirrhosis and with compensated cirrhosis.[40] Four were considered Phase 3 in design; two of which were comparative to either placebo or DCV/SOF.[41] All other trials were open-label and four of the trials were single-arm with no randomization and were not designed to test a hypothesis. SVR12 was the primary outcome in all of the trials. Overall, there were few black patients (6%), fewer cirrhotics (13%) and in the non-cirrhotic trials, the majority had F0-F1 stage disease. Many of these remain unpublished and are only available as poster abstracts. . The primary source for data analysis comes from the FDA review documents.[41]

DAA Treatment-Experienced

Data to support G/P in DAA-treatment experienced comes from one phase 2 trial with two parts (MAGELLAN-1 part 1 and 2) (Table 8). Part 1 is an open-label, phase 2 dose-ranging study comparing 3 arms of G/P in HCV GT 1 patients without cirrhosis and with prior DAA treatment experience. [42] The lower dose arm was halted early, and all remaining patients were randomized to either G/P or G/P + RBV for 12 weeks (n=50) at the dose that was FDA approved (300 mg/120 mg). This study has many serious limitations and flaws including high risk of selection, performance, and detection bias due to the open-label design, no information on how patients were randomized, unbalanced baseline characteristics, and lack of a comparator group. A dose-response was not clear since the SVR12 rate was higher in the low dose group (100%; 6/6) compared to the high dose group (86%; 19/22), but the small population limits ability to make any conclusions. Additionally, the most common prior DAA-containing regimen was boceprevir plus PEG/RBV (n=10) and telaprevir plus PEG/RBV (n=8), both of which are no longer used in clinical practice. A total of 8 patients received LDV/SOF, and 8 received SOF/SMV. Sixty four percent (33/50) of patients had a baseline fibrosis stage of F0-F1. Overall, SVR was achieved in 92% (46/50; 95% CI 81-97) of patients. The SVR in the higher dose group without RBV was 86% (19/22; 95% CI 67-95) and was 95% (21/22; 95% CI 78-99) in the high dose group with RBV. The sample size was not large enough to determine the impact of adding RBV to G/P.

MAGELLAN-1, part 2 was a multicenter, randomized, open label trial comparing G/P for 12 (n=44) or 16 weeks (n=47) in patients with GT 1 or 4 and prior DAA treatment failure with either a NS5A and/or NS3 protease inhibitor, including those with compensated cirrhosis.[43] This is the only trial that enrolled subjects who were treatment experienced with a NS5A inhibitor and/or NS3/4A protease inhibitor. Almost all of the patients were GT 1 (74% with GT 1a and 21% with GT 1b). The overall SVR12 was 89% (39/44) in those receiving G/P for 12 weeks and 91% (43/47) in those receiving therapy for 16 weeks. There were 4 patients

in the 16-week group with virologic failure and zero with relapse compared to 1 patient with virologic failure and 4 with relapse in the 12-week group. When broken down based on prior DAA therapy, SVR rates were lower in those patients who had been on both a NS3 protease inhibitor and NS5A inhibitor (Table 8). This study is only available in poster abstract form and cannot be fully assessed for quality. The study was not designed to make definitive conclusions based on prior DAA regimen.

There is insufficient evidence with G/P for DAA-treatment experienced patients with cirrhosis, hepatitis B virus (HBV), HIV coinfection, genotypes other than GT 1, or discontinuation of a previous treatment regimen due to non-adherence.

Table 8: SVR rates in clinical trials including treatment-experienced GT 1 patients treated with G/P:

	MAGELLAN-1 part 2		**MAGELLAN-1 part 1**	
	G/P x 12 weeks	**G/P x 16 weeks**	**G/P x 12 weeks**	**G/P + RBV x 12 weeks**
Overall	89% (39/44) (95% CI 76 to 95)	91% (43/47) (95% CI 80 to 97)	86% (19/22) (95% CI 66 to 95)	95% (21/22)
Compensated Cirrhosis	93% (14/15)	75% (9/12)	Excluded	Excluded
Without Cirrhosis	N/A	N/A	N/A	N/A
Prior NS3 PI	100% (14/14/)	100% (13/13)	N/A	N/A
Prior NS5A inhibitor	88% (14/16)	94% (17/18)	N/A	N/A
Prior NS3 PI + NS5A	79% (11/14)	81% (13/16)	N/A	N/A

Treatment-Naïve (and PEG/RBV treatment-experienced):

Efficacy of G/P in treatment naïve GT1-6 patients without cirrhosis was evaluated in two phase 2 open-label, multicenter, dose-ranging trials evaluating G/P for 8 and 12 weeks that excluded patients with HBV, HIV and cirrhosis (n=449).[44] These studies helped determine the optimal dose based on higher efficacy of the higher-dose in GT 3 patients. The 8-week treatment course resulted in 97-98% SVR12 in those with GT 1, 2, or 3.

Additionally, G/P was studied in four phase 3 trials and two phase 2 trials (Tables 9 and 10). However, only three of these has been published and only one can be fully assessed for quality[45] (see evidence table). All of the phase 3 trials included treatment-naïve patients, or those who did not respond to treatment with PEG/RBV or SOF + RBV +/- PEG. Treatment with a DAA other than SOF was not included. Four of the clinical trials excluded those with cirrhosis (Table 9). The majority of patients included in these trials had fibrosis stage F0-F1 (~80%) and thus limits applicability to the Oregon Medicaid population. All trials except ENDURANCE 1 excluded HIV co-infection, and all trials excluded HBV and those with CrCl less than 50 mL/min. The majority of patients were white and had more mild disease. They were all open-label other than ENDURANCE-2 in GT 2 HCV, which had a placebo comparator. ENDURANCE-3 was the only trial to include an active control group (SOF + DCV). Information on SVR24 is not available at this time. An 8-week regimen was included in GT 1 and GT 3. Trials including GT 2 and GT 4, 5, or 6 only included a 12-week arm of G/P.

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ENDURANCE-1 was the largest study and demonstrated similar SVR12 rates with 8 weeks of therapy in GT 1 compared to 12 weeks (99.1% vs. 99.7%). The primary objective was to demonstrate on-inferiority of the 12 week regimen to a historical control of 97% SVR12 with a 6% non-inferiority margin.[41] The FDA did not agree with this approach without an active comparator and analyzed it based on superiority, evaluating the lower bound of the 95% CI compared to clinically acceptable threshold of 91%.[41] Both the 8 and 12 week arms demonstrating superiority. This study included 33 patients with HIV co-infection, and all 33 achieved SVR12 regardless of duration.

ENDURANCE-2 was a double blind, placebo controlled trial resulting in superiority of 12 weeks of G/P (n=202) compared to a historical control SVR 12 of 95% with 12 weeks of SOF/RBV.[46] The majority of patients (70%) were treatment naïve and had F0-F1 stage disease. The SVR12 rate was 99.5% (195/196; 95% CI 98.5-100). There were no virologic failures. Information on how the study was blinded or randomized is not available at this time as the study supplement has not been published yet and only an unedited version was available. [46] Therefore, a quality assessment was not possible. Patients were also randomized to placebo that then received open-label treatment with G/P. Neither SVR24 data nor SVR12 rates for the deferred treatment placebo group is also not available. It is unclear why an 8-week course was not evaluated in the phase 3 trial. In SURVEYOR-II, part 4, an open-label single arm trial, HCV GT 2 patients were treated with 8 weeks of G/P and 142 of 145 patients experienced a SVR12 (98%; 95% CI 94.1 to 99.3) with two virologic failures.[46] Both 8- and 12-week regimens were non-inferior to the standard of care SVR of 95%. ENDURANCE-4 was designed identically but included those with GT 4-6 with the majority of patients having GT 4 CHC. [46] In those with GT4, SVR12 was achieved in 93% (43/36) of patients who received 8 weeks of therapy and 99% of those who received 12 weeks (120/121).

ENDURANCE-3 was the only trial including an active control, SOF + DCV for 12 weeks and included GT 3 patients without cirrhosis. The study also included an 8-week arm of G/P; however, this was a non-randomized arm added after the completion of the study. Both the 8- and 12-week G/P regimens met non-inferiority criteria to SOF + DCV with SVR12 rates of 95-97%. However, the 8-week arm did not demonstrate superiority over the 92% historical threshold decided on by the FDA review team.[41] Additional phase 2 data demonstrated an SVR12 in 28 our of 29 GT3 treatment-naïve patients (97%; 95% CI 82.8 to 99.4) who received 8 weeks of treatment. The FDA concluded sufficient data that 8-weeks was comparable to 12 weeks for those with GT 3 and did not identify a specific subgroup that seemed to benefit from 12 weeks of therapy.

Table 9. Phase 2 and 3 trials in treatment naïve non-cirrhotic GT 1-6 patients

	Clinical Trials			
	ENDURANCE-1	**ENDURANCE-2**	**ENDURANCE-3**	**ENDURANCE-4**
Study Design	Open-label, MC, phase 3, non-inferiority	DB, PC, RCT, phase 3	Open-label, partially randomized*, active-control, phase 3	MC, open-label, single arm, phase 2
Comparison	G/P 8 weeks (n=351) vs. G/P for 12 weeks (n=352)	G/P x 12 weeks (n=202) vs. placebo (deferred treatment)	G/P 12 weeks (n=233) vs. SOF + DCV 12 weeks (n=115) versus G/P 8 weeks (n=157)	G/P x 12 weeks (n=121)

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		(n=100) vs. historical rate 95%		
Genotypes included	GT 1	GT 2	GT 3	GT 4, 5, or 6
Cirrhosis Inclusion	Non-cirrhosis only	Non-cirrhosis only	Non-cirrhosis only	Non-cirrhosis only
Duration	8 vs. 12 weeks	12 weeks	8 weeks	8 weeks
Fibrosis Stage	85% F0-F1	80% F0-F2	83% F0-F1	86% F0-F1
Publication Status	Unpublished; poster only	Unpublished; poster only	Unpublished; poster only	Unpublished; poster only
SVR 12	99.1% (332/335) with 8 weeks vs. 99.7% (331/332) with 12 weeks	99.5% (195/196; 95% CI 98.5-100)	G/P 12 weeks: 95% (222/233) DCV + SOF: 97% (111/115) G/P 8 weeks 95% (149/157)	GT 4: 98.7%% (75/76) GT 5: 100% (26/26) GT 6: 100% (19/19)
*non-randomized 3rd arm with G/P for 8 weeks was added				

Three additional trials included those with compensated cirrhosis (Table 10), one of which has been published and available at the time for quality assessment (see evidence table). These were both open-label, single arm, non-randomized, multicenter trials. The EXPEDITION-1 trial was an open-label, single-arm, phase 2 trial with many limitations.[45] Although it was claimed to be phase 3, it lacked a formal hypothesis and was evaluated by the FDA as phase 2. It evaluated 12 weeks of G/P in patients (n=146) with GT 1, 2, 4, 5 or 6 with compensated cirrhosis (Child-Pugh A only). Patients with GT 3 HCV, decompensated cirrhosis, Child-Pugh B or C, HIV, HBV, or other sources of liver disease were excluded. Due to the study design (open-label and non-randomized), there is a high risk of bias in this trial. Nonetheless, the magnitude of effect was significant, and 99% (145/146) of patients achieved an SVR12 (95% CI 98-100).[45] The study did not report SVR24 rates. SVR was achieved regardless of baseline RAVs. This trial excluded those with GT 3 which is a more difficult patient population to treat and results may appear more favorable without this population. Data in this population comes from a phase 3 open-label study including treatment naïve and treatment experienced patients with PEG/RBV or SOF with GT3 without cirrhosis or with compensated cirrhosis. [48] This study was not designed to test a formal hypothesis. Subjects with compensated cirrhosis were treated for 12 weeks if treatment naïve and 16 weeks of treatment experienced. SVR rates ranged from 90.9% to 96.6% and were higher with 16 weeks (21/22; 95%; 95% CI 78.2 to 99.2) compared to 12 weeks (20/22; 90.0%; 95% CI 72.2 to 9.5). The FDA approved 16 weeks, regardless of cirrhosis, because the risk of relapse was about 4% higher (8.4% vs. 4.5%) in those treated with 12- and 16- week durations, respectively. Since this group wasn't included in the phase 3 follow up trials, the optimal treatment duration and the benefit of RBV for GT 3 patients with compensated cirrhosis remains unclear.

Almost all of the G/P trials excluded those with renal impairment (CrCl <50mL/min). However, G/P is currently approved for those with kidney disease based on the EXPEDITION-4 trial in patients (n=104) with stage 4 or 5 chronic kidney disease (CKD).[49] This trial included treatment-naïve, PEG/RBV and/or SOF treatment-experienced patients with GT 1-6 CHC. However, patients with GT 3 who were treatment experienced were excluded from this trial. Twenty patients (19%) also had compensated cirrhosis and 82% were hemodialysis dependent. Sixty (58%) of patients were treatment naïve and only 2 patients had previous treatment

with SOF. The overall SVR12 rate was 98% (102/104; 95% CI 95-100%). No patients had a virologic failure and the SVR24rate was 95% (100/104; 95% CI 95-100%). This study had a high risk of selection, detection and performance bias due to its open-label, single arm design with no comparator or randomization.

Table 10. Phase 2 and 3 G/P trials in treatment naïve and treatment experienced with PEG/RBV or SOF with compensated cirrhosis

	Clinical Trials		
	EXPEDITION-1	**EXPEDITION-4**	**SURVEYOR-2, Part 3**
Study Design	Open-label, single-arm, MC, phase 2	Open-label, single-arm, MC, phase 3	Open-label, non-randomized, MC, phase 3
Comparator	None	None	None
Genotypes included	GT 1, 2, 4, 5, 6 (n=146)	GT 1-6 (n=104)	GT 3 treatment naïve (n=40) and GT 3 PEG/RBV treatment experienced (n=47)
Cirrhosis Inclusion	Compensated Cirrhosis (Child-Pugh A)	Non-Cirrhosis or compensated cirrhosis and stage 4/5 CKD	Compensated cirrhosis
Duration	12 weeks	12 weeks	12 weeks (treatment-naïve) – 16 weeks (treatment experienced)
Fibrosis Stage/patient population	Compensated Cirrhosis	19% (20) with compensated cirrhosis; 82% hemodialysis dependent	Compensated cirrhosis (Child-Pugh A only) Treatment history: 47% PEG, 53% SOF
Publication Status	Published[45]	Published[49]	Published[48]
SVR 12	99% (145/146); 95% CI 98-100	98% (102/104); 95% CI 95-100	Treatment naïve: 98% (39/40); 95% CI 87-99 Treatment experienced: 96% (45/47); 95% CI 86-99

Clinical Safety:

The most common adverse events in clinical trials were fatigue (11%), headache (13%), and nausea (8%).[40] There were low discontinuations due to adverse events (0.1%) or serious adverse events in clinical trials.

There were two controlled trials of G/P (ENDURANCE-2 and ENDURANCE-3). ENDURANCE-2 had a placebo group and adverse reactions that occurred in >5% of patients and more than placebo included headache (9% vs. 6%), nausea (6% vs. 2%) and diarrhea (5% vs. 2%).[40] ENDURANCE-3 included an active comparator group with DCV + SOF and adverse reactions reported in ≥5% of treatment-naïve adults without cirrhosis are included in Table 11.

Table 11: Adverse reactions occurring in ≥5% in treatment-naïve adults without cirrhosis in ENDURANCE-3:

	G/P x 8 weeks (n=157)	G/P x 12 weeks (n=233)	DCV + SOF x 12 weeks (n=115)
Headache	16%	17%	15%
Fatigue	11%	14%	12%
Nausea	9%	12%	12%

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Diarrhea	7%	3%	2%

There are potential drug-drug interactions that need to be accounted for with G/P since they are substrates of P-glycoprotein inhibitors of CYPP450 enzymes. Treatment with G/P is not recommended for those with moderate or severe hepatic impairment (Child-Pugh B or C) due to a presumed class effect of the protease inhibitors and the increased risk of serious liver injury in those with underlying advanced liver disease.

Table 12. Pharmacology and Pharmacokinetic Properties.

Parameter	Glecaprevir	Pibrentasvir
Mechanism of Action	HCV NS3/4A protease inhibitor	NS5A inhibitor
Oral Bioavailability	N/A	N/A
Distribution and Protein Binding	97.5% protein bound	>99.9% protein bound
Elimination	Feces (92.1%), urine (0.7%)	Feces (96.6%)
Half-Life	6 hours	13 hours
Metabolism	Secondary to CYP3A	None

Abbreviations: HCV: hepatitis C virus, N/A: not available

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Hepatocellular Carcinoma
2) Mortality
3) Liver Transplant
4) Decompensated Liver Disease
5) Discontinuation Rates Due to Adverse Events
6) Severe Adverse Events
6) Quality of Life

Primary Study Endpoint:
2) Sustained Virologic Response at 12 weeks post-treatment (SVR12)

Table 13. Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. .Forns et al. EXPEDITION-1[45]	1. G/P X 12 weeks	Demographics: Treatment naïve, GT 1, 2, 3, 4 or 6 with compensated	ITT: 1. 146	SVR12: 1. 145/146; 99% (95% CI 98-100)	N/A	Discontinuations due to adverse events: 1. 0	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: high; open-label, single-arm, non-randomized Performance Bias: high; open-label

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Single-arm, open-label, MC, phase 3		cirrhosis (Child-Pugh A) Key Inclusion Criteria: >18 y/o, treatment naïve, compensated cirrhosis. Key Exclusion Criteria: decompensated cirrhosis, Child-Pugh B or C unstable psychiatric disease, significant cardiac disease, malignancy, abnormal AST/ALT, bilirubin > 3 ULN, plts < 60,000, HgA1C > 8.5%, CrCl < 50mL/min, Hg < 12 albumin < 3, chronic liver disease of non-HCV origin, HBV, HIV, alcohol or drug abuse within previous 6 months	Attrition: 1. 0					Detection Bias: high; open-label Attrition Bias: unclear; low attrition overall Reporting Bias: unclear; full protocol not available **Applicability**: Patient: Majority (60%) were GT1, 82% white, 75% treatment-naïve. Extensive exclusion criteria limits generalizability. GT 3, a more difficult population to treat, excluded. Intervention: N/A Comparator: No active comparator Outcomes: SVR12 remains an invalidated surrogate outcome. Setting: Multicenter: Belgium , Canada, Germany, South Africa, Spain, U.S. Sponsored by Abbvie. Abbvie was involved in data collection, statistical analysis, and writing of the manuscript.

Abbreviations: AE = adverse events; ALT = alanine aminotransferase; ; ARI = absolute risk increase; ARR = absolute risk reduction; CI = confidence interval; CKD = chronic kidney disease; CrCl = creatinine clearance; CV = cardiovascular; DB = double-blind; DAA = direct acting antiviral; D/C = discontinue; DM = diabetes mellitus; DTG = deferred treatment group; EF = ejection fraction; FAS = full analysis set; FDA = U.S. Food and Drug Administration; GT = genotype;; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; h/o = history of; HG = hemoglobin; MC = multi-centered; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; OR = odds ratio; PC = placebo-controlled; PBO = placebo;; PG = parallel group; PP = per protocol; PT=prothrombin time; RBV = ribavirin; RCT = randomized controlled trial; RR = relative risk; RRR = relative risk reduction; SAE = serious adverse event; SE = standard error; SVR12 = sustained virologic response at 12 weeks after therapy completed; TE = treatment experienced; TN = treatment naïve; Tx = treatment; ULN = upper limit of normal; wk = weeks; wt = weight; y = years; µL = microliters.

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Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	DAKLINZA	DACLATASVIR DIHYDROCHLORIDE	Y
ORAL	TABLET	DAKLINZA	DACLATASVIR DIHYDROCHLORIDE	Y
ORAL	TABLET	HARVONI	LEDIPASVIR/SOFOSBUVIR	Y
ORAL	TABLET	SOVALDI	SOFOSBUVIR	Y
ORAL	TAB DS PK	VIEKIRA PAK	OMBITA/PARITAP/RITON/DASABUVIR	N
ORAL	TABLET	TECHNIVIE	OMBITASVIR/PARITAPREV/RITONAV	N
ORAL	TABLET	ZEPATIER	ELBASVIR/GRAZOPREVIR	N
ORAL	CAPSULE	OLYSIO	SIMEPREVIR SODIUM	N

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Appendix 2: OVID Search Results

# ▲	Searches	Results	Type	Actions	Annotations
1	Hepatitis C, Chronic/ or Antiviral Agents/ or Hepatitis C/	88131	Advanced	Display Results | More	
2	direct acting antivirals.mp.	717	Advanced	Display Results | More	
3	sofosbuvir.mp. or Sofosbuvir/	820	Advanced	Display Results | More	
4	daclatasvir.mp.	326	Advanced	Display Results | More	
5	ledipasvir.mp.	262	Advanced	Display Results | More	
6	ombitasvir.mp.	133	Advanced	Display Results | More	
7	dasabuvir.mp.	118	Advanced	Display Results | More	
8	paritaprevir.mp.	119	Advanced	Display Results | More	
9	elbasvir.mp.	43	Advanced	Display Results | More	
10	grazoprevir.mp.	41	Advanced	Display Results | More	
11	voxilaprevir.mp.	1	Advanced	Display Results | More	
12	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	1610	Advanced	Display Results | More	
13	1 and 12	1546	Advanced	Display Results | More	
14	limit 13 to (english language and humans and yr="2016 -Current" and (clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or meta analysis or practice guideline or randomized controlled trial or systematic reviews))	68	Advanced	Display Results | More	

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Appendix 3: Summary of Randomized Controlled Trials

Randomized Controlled Trials:

After initial review, 23 trials were manually reviewed from the literature search. The majority of trials were excluded due to wrong study design, wrong comparator, poor quality, or unapproved medication. Trials supporting the 2 new drug approvals are discussed in the new drug sections. The remaining two trials are briefly described in the table below.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Results (Primary Outcome; SVR12)	
Leroy, 2016[51] RCT, phase III, open-label	DCV/SOF + RBV for 12 or 16 weeks	GT 3 with advanced fibrosis or compensated cirrhosis	SVR12: 12 wk: 21/24 (87.5%; 95% CI 67.6-97.3) 16 wk: 24/26 (92.3%; 95% CI 74.9-99.1)	
Kwo, 2017[52] Phase III, open-label, RCT	EBR/GZR x 12 weeks vs. EBR/GZR + RBV x 12 weeks vs. EBR/GZR x 16 weeks vs. EBR/GZR + RBV x 16 week	GT 1, 4, or 6 with or without cirrhosis, previously treated with PEG/RBV (n=420)	SVR12: 12 weeks: EBR/GZR: 92.4% EBR/GZR + RBV: 94.2%	SVR12: 16 weeks: EBR/GZR: 92.4% EBR/GZR + RBV: 98.1%

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Appendix 4: Abstracts of Randomized Controlled Trials:

1. Leroy V, Anugs P, Bronowicki, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). *Hepatology*. 2016 May;63(5):1430-41.

Patients with hepatitis C virus (HCV) genotype 3 infection, especially those with advanced liver disease, are a challenging population in urgent need of optimally effective therapies. The combination of daclatasvir (DCV; pangenotypic nonstructural protein 5A inhibitor) and sofosbuvir (SOF; nucleotide nonstructural protein 5B inhibitor) for 12 weeks previously showed high efficacy (96%) in noncirrhotic genotype 3 infection. The phase III ALLY-3+ study (N = 50) evaluated DCV-SOF with ribavirin (RBV) in treatment-naïve (n = 13) or treatment-experienced (n = 37) genotype 3-infected patients with advanced fibrosis (n = 14) or compensated cirrhosis (n = 36). Patients were randomized 1:1 to receive open-label DCV-SOF (60 + 400 mg daily) with weight-based RBV for 12 or 16 weeks. The primary endpoint was sustained virological response at post-treatment week 12 (SVR12). SVR12 (intention-to-treat) was 90% overall (45 of 50): 88% (21 of 24) in the 12-week (91% observed) and 92% (24 of 26) in the 16-week group. All patients with advanced fibrosis achieved SVR12. SVR12 in patients with cirrhosis was 86% overall (31 of 36): 83% (15 of 18) in the 12-week (88% observed) and 89% (16 of 18) in the 16-week group; for treatment-experienced patients with cirrhosis, these values were 87% (26 of 30), 88% (14 of 16; 93% observed), and 86% (12 of 14), respectively. One patient (12-week group) did not enter post-treatment follow-up (death unrelated to treatment). There were 4 relapses (2 per group) and no virological breakthroughs. The most common adverse events (AEs) were insomnia, fatigue, and headache. There were no discontinuations for AEs and no treatment-related serious AEs.

CONCLUSION:
The all-oral regimen of DCV-SOF-RBV was well tolerated and resulted in high and similar SVR12 after 12 or 16 weeks of treatment among genotype 3-infected patients with advanced liver disease, irrespective of past HCV treatment experience.

2. Kwo P, Gane EJ, Peng CY, Pearlman B. Effectiveness of Elbasvir and Grazoprevir Combination, With or Without Ribavirin, for Treatment-Experienced Patients With Chronic Hepatitis C Infection. *Gastroenterology*. 2017 Jan;152(1):164-175.e4. doi: 10.1053/j.gastro.2016.09.045. Epub 2016 Oct 5.

BACKGROUND & AIMS:
Patients infected with hepatitis C virus (HCV) genotype 1, 4, or 6, with or without cirrhosis, previously treated with peg-interferon and ribavirin, are a challenge to treat. We performed a phase 3 randomized controlled open-label trial to assess the effects of 12 or 16 weeks of treatment with once-daily elbasvir (an HCV NS5A inhibitor, 50 mg) and grazoprevir (an HCV NS3/4A protease inhibitor, 100 mg), in a fixed-dose combination tablet, with or without twice-daily ribavirin, in this patient population.

METHODS:
We analyzed data from 420 patients (35% with cirrhosis, 64% with a null or partial response to peg-interferon and ribavirin) who were randomly assigned (1:1:1:1) to groups given elbasvir and grazoprevir once daily, with or without twice-daily ribavirin, for 12 or 16 weeks, at 65 study centers in 15 countries in Europe, Asia, and Central and North America. Randomization was stratified by cirrhosis status and type of peg-interferon and ribavirin treatment failure. HCV

RNA was measured using COBAS TaqMan v2.0. The primary end point was HCV RNA <15 IU/mL, 12 weeks after completion of treatment (SVR12). We aimed to determine whether the proportion of patients achieving an SVR12 in any group was greater than the reference rate (58%).

RESULTS:
With 12 weeks of treatment, an SVR12 was achieved by 92.4% of patients given elbasvir and grazoprevir and 94.2% of patients given elbasvir and grazoprevir with ribavirin. With 16 weeks of treatment, an SVR12 was achieved by 92.4% of patients given elbasvir and grazoprevir and 98.1% of patients given elbasvir and grazoprevir with ribavirin. Among patients treated for 12 weeks without ribavirin, virologic failure occurred in 6.8%, 0%, and 12.5% of patients with HCV genotype 1a, 1b, or 4 infection, respectively. Among patients given elbasvir and grazoprevir for 12 weeks, virologic failure occurred in 0% of patients infected with HCV genotypes 1 and 4 who relapsed after completing peg-interferon and ribavirin, and 7.5% infected with HCV genotypes 1 and 4, respectively, with a null or partial response to peg-interferon and ribavirin. Among patients treated for 16 weeks who received ribavirin, there were no incidences of virologic failure. Common adverse events were fatigue (23.1%), headache (19.8%), and nausea (11.0%).

CONCLUSIONS:
The combination tablet of elbasvir and grazoprevir, with or without ribavirin, was highly efficacious in inducing an SVR12 in patients with HCV genotype 1, 4, or 6 infection failed by previous treatment with peg-interferon and ribavirin, including patients with cirrhosis and/or a prior null response. The treatment was generally well tolerated. ClinicalTrials.gov Number: NCT02105701.

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

Appendix 5: Highlights of Prescribing Information for Vosevi®

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VOSEVI safely and effectively. See full prescribing information for VOSEVI.

VOSEVI™ (sofosbuvir, velpatasvir, and voxilaprevir) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV
See full prescribing information for complete boxed warning.

Hepatitis B virus (HBV) reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.1)

----------INDICATIONS AND USAGE----------

VOSEVI is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, velpatasvir, an HCV NS5A inhibitor, and voxilaprevir, an HCV NS3/4A protease inhibitor, and is indicated for the treatment of adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have (1, 2.2, 14):

- genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor.
- genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.
  - Additional benefit of VOSEVI over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.

----------DOSAGE AND ADMINISTRATION----------

- Testing prior to the initiation of therapy: Test all patients for HBV infection by measuring HBsAg and anti-HBc. (2.1)
- Recommended dosage: One tablet (400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir) taken orally once daily with food. (2.2)
- See recommended treatment regimen and duration in table below (2.2):

Genotype	Patients Previously Treated with an HCV Regimen Containing:	VOSEVI Duration
1, 2, 3, 4, 5, or 6	An NS5A inhibitor[a]	12 weeks
1a or 3	Sofosbuvir without an NS5A inhibitor[b]	12 weeks

a. In clinical trials, prior NS5A inhibitor experience included daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir.
b. In clinical trials, prior treatment experience included sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir).

- A dosage recommendation cannot be made for patients with severe renal impairment or end stage renal disease (2.3)
- VOSEVI is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 400 mg sofosbuvir, 100 mg velpatasvir, and 100 mg voxilaprevir (3)

----------CONTRAINDICATIONS----------

Coadministration with rifampin. (4)

----------WARNINGS AND PRECAUTIONS----------

- Risk of Hepatitis B virus reactivation: Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated. (5.1)
- Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone with VOSEVI, a sofosbuvir-containing regimen, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with VOSEVI is not recommended. In patients without alternative viable treatment options, cardiac monitoring is recommended. (5.2, 7.3)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with VOSEVI for 12 weeks were headache, fatigue, diarrhea, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- P-gp inducers and/or moderate to potent CYP inducers (e.g., St. John's wort, carbamazepine): May decrease concentrations of sofosbuvir, velpatasvir, and/or voxilaprevir. Use of VOSEVI with P-gp inducers and/or moderate to potent CYP inducers is not recommended (5.3, 7)
- Consult the full prescribing information prior to use for potential drug interactions (4, 5.2, 5.3, 7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2017

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

Appendix 6: Highlights of Prescribing Information for Mavyret®

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MAVYRET safely and effectively. See full prescribing information for MAVYRET.

MAVYRET™ (glecaprevir and pibrentasvir) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV
See full prescribing information for complete boxed warning.
Hepatitis B virus (HBV) reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.1)

INDICATIONS AND USAGE

MAVYRET is a fixed-dose combination of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor, and is indicated for the treatment of patients with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis and with compensated cirrhosis (Child-Pugh A). MAVYRET is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. (1)

DOSAGE AND ADMINISTRATION

- Testing Prior to the Initiation of Therapy: Test all patients for HBV infection by measuring HBsAg and anti-HBc. (2.1)
- Recommended dosage: Three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) taken orally once daily with food. (2.2)
- See recommended treatment duration in tables below. (2.2)

Treatment-Naïve Patients

HCV Genotype	Treatment Duration	
	No Cirrhosis	Compensated Cirrhosis (Child-Pugh A)
1, 2, 3, 4, 5, or 6	8 weeks	12 weeks

Treatment-Experienced Patients

		Treatment Duration	
HCV Genotype	Patients Previously Treated With a Regimen Containing:	No Cirrhosis	Compensated Cirrhosis (Child-Pugh A)
1	An NS5A inhibitor[1] without prior treatment with an NS3/4A protease inhibitor	16 weeks	16 weeks
	An NS3/4A PI[2] without prior treatment with an NS5A inhibitor	12 weeks	12 weeks
1, 2, 4, 5, or 6	PRS[3]	8 weeks	12 weeks
3	PRS[3]	16 weeks	16 weeks

1. In clinical trials, subjects were treated with prior regimens containing ledipasvir and sofosbuvir or daclatasvir with pegylated interferon and ribavirin.
2. In clinical trials, subjects were treated with prior regimens containing simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin
3. PRS=Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.

- HCV/HIV-1 co-infection and patients with any degree of renal impairment: Follow the dosage recommendations in the tables above. (2.2)
- Hepatic Impairment: MAVYRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B); and is contraindicated in patients with severe hepatic impairment (Child-Pugh C). (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg glecaprevir and 40 mg pibrentasvir. (3)

CONTRAINDICATIONS

- Patients with severe hepatic impairment (Child-Pugh C). (4, 8.7, 12.3)
- Coadministration with atazanavir and rifampin. (4)

WARNINGS AND PRECAUTIONS

Risk of Hepatitis B Virus Reactivation: Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated. (5.1)

ADVERSE REACTIONS

In subjects receiving MAVYRET, the most commonly reported adverse reactions (greater than 10%) are headache and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Carbamazepine, efavirenz, and St. John's wort may decrease concentrations of glecaprevir and pibrentasvir. Coadministration of carbamazepine, efavirenz containing regimens, and St. John's wort with MAVYRET is not recommended. (5.2)
Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2017

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

Appendix 7: Prior Authorization Criteria

Hepatitis C Direct-Acting Antivirals

Goals:

- Approve use of cost-effective treatments supported by the medical evidence.
- Provide consistent patient evaluations across all hepatitis C treatments.
- Ensure appropriate patient selection based on disease severity, genotype, and patient comorbidities.

Length of Authorization:

- 8-16 weeks

Requires PA:

- All direct-acting antivirals for treatment of Hepatitis C

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of chronic Hepatitis C infection?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is expected survival from non-HCV-associated morbidities more than 1 year?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.

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Approval Criteria		
4. Has <u>all</u> of the following pre-treatment testing been documented: a. Genotype testing in past 3 years; b. Baseline HCV RNA level in past 6 months; c. Current HIV status of patient d. Current HBV status of patient e. Pregnancy test in past 30 days for a woman of child-bearing age; <u>and</u> f. History of previous HCV treatment and outcome? Note: Direct-acting antiviral agents can re-activate hepatitis B in some patients. Patients with history of HBV should be monitored carefully during and after treatment for flare-up of hepatitis. Prior to treatment with a DAA, all patients should be tested for HBsAG, HBsAb, and HBcAB status.	**Yes:** Record results of each test and go to #5 Note: If the patient has HIV or HBV co-infection, it is highly recommended that a specialist be consulted prior to treatment.	**No**: Pass to RPh. Request updated testing.
5. Which regimen is requested?	Document and go to #6	
6. Does the patient have HIV coinfection and is under treatment by a specialist with experience in HIV? Note: persons with HIV/HCV coinfection are at risk for rapidly progressing fibrosis	**Yes:** Go to #11	**No:** Go to #7

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Approval Criteria		
7. Does the patient have: a) A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]) to indicate portal fibrosis with septa (METAVIR F2) advanced fibrosis (METAVIR F3) or cirrhosis (METAVIR F4); **OR** Clinical, radiologic or laboratory evidence of complications of cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma)?	**Yes:** Go to #10 Note: Other imaging and blood tests are not recommended based on evidence of poor sensitivity and specificity compared to liver biopsy. However, if imaging testing is not regionally available, a serum test (FIBROSpect II; Fibrometer; enhanced liver fibrosis [ELF], Fibrosure) can be used to confirm METAVIR F2 or greater but cannot be used for denial. For results falling in a range (e.g. F1 to F2), fibrosis stage should be categorized as the higher F stage for the purpose of treatment, or require one additional, more specific test (per HERC AUROC values http://www.oregon.gov/OHA/HPA/CSI-HERC/Pages/Evidence-based-Reports-Blog.aspx?View=%7b2905450B-49B8-4A9B-AF17-5E1E03AB8B6B%7d&SelectedID=237) to be obtained to determine the stage of fibrosis. However, additional testing cannot be limited to biopsy. After one additional test, if a range still exists, the highest F score in the range will be used for determining coverage.	**No:** Go to #8

Approval Criteria		
8. Does the patient have one of the following extrahepatic manifestations of Hepatitis C (with documentation from a relevant specialist that their condition is related to HCV)? a) Lymphoproliferative disease, including type 2 or 3 cryoglobulinemia with end-organ manifestations (i.e., leukocytoclastic vasculitis); or b) Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis; or c) Porphyria cutanea tarda or lichen planus d) Lymphomas (B-cell non-Hodgkin lymphoma) e) Type 2 Diabetes with insulin resistance f)	**Yes:** Go to #10	**No:** Go to #9
9. Is the patient in one of the following transplant settings: a) Listed for a transplant and treatment is essential to prevent recurrent hepatitis C infection post-transplant; or b) Post solid organ transplant?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. If METAVIR F4: Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist? **OR** If METAVIR F3: Is the regimen prescribed by, OR is the patient in the process of establishing care with or in consultation with a hepatologist, gastroenterologist, or infectious disease specialist? **OR** If METAVIR ≤F2: The regimen does not need to be prescribed by or in consultation with a specialist.	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness. Forward to DMAP for further manual review to determine appropriateness of prescriber.

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Approval Criteria		
11. In the previous 6 months: a) Has the patient actively abused alcohol (>14 drinks per week for men or >7 drinks per week for women or binge alcohol use (>4 drinks per occasion at least once a month); OR b) Has the patient been diagnosed with a substance use disorder; OR c) Is the prescriber aware of current alcohol abuse or illicit injectable drug use?	**Yes:** Go to #12	**No:** Go to #13
12. Is the patient enrolled in a treatment program under the care of an addiction/substance use treatment specialist?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.
13. Will the patient and provider comply with all case management interventions and adhere to monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load?	**Yes**: Go to #14	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the prescribed drug: a) Elbasvir/grazoprevir for GT 1a infection; or b) Daclatasvir + sofosbuvir for GT 3 infection?	**Yes**: Go to #15	**No:** Go to #16
15. Has the patient had a baseline NS5a resistance test that documents a resistant variant to one of the agents in #16? Note: Baseline NS5A resistance testing is required.	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #16 Document test and result.
16. Is the prescribed regimen include a NS3/4a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir)?	**Yes:** Go to #17	**No:** Go to #18

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Approval Criteria		
17. Does the patient have moderate-severe hepatic impairment (Child-Pugh B or Child-Pugh C)?	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #18
18. Is the prescribed regimen for the retreatment after failure of a DAA due to noncompliance or lost to follow-up?	**Yes:** Pass to RPh; Deny and refer to medical director for review	**No:** Go to #19
19. Is the prescribed drug regimen a recommended regimen based on the patient's genotype, treatment status (retreatment or treatment naïve) and cirrhosis status (see **Table 1**)?	**Yes:** Approve for 8-16 weeks based on duration of treatment indicated for approved regimen	**No:** Pass to RPh. Deny; medical appropriateness.

Table 1: Recommended Treatment Regimens for Chronic Hepatitis C.

Treatment History	Cirrhosis Status	Recommended Regimen
Genotype 1		
DAA-Treatment naive	Non-cirrhotic	EBR/GZR x 12 weeks** SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated Cirrhosis	EBR/GZR x 12 weeks** SOF/VEL x 12 weeks G/P x 12 weeks
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 week
Treatment experienced (Prior PEG/RBV)	Non-cirrhotic	EBR/GZR x 12 weeks** SOF/VEL x 12 weeks

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		G/P x 8 weeks
	Compensated cirrhosis	EBV/GRZ 12weeks** SOF/VEL x 12 weeks G/P x 12 weeks
Treatment Experienced (Prior sofosbuvir)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks SOF/VEL/VOX x 12 weeks (GT 1 a only without tx h/o NS5A inhibitor) G/P x 12 weeks
Treatment Experienced (Prior NS3A/4A inhibitor)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks EBR/GZR + RBV x 12 weeks** G/P x 12 weeks
Treatment Experienced (prior NS5A-containing regimen)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks G/P x 16 weeks
Genotype 2		
Naïve	Non-cirrhotic	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
	Decompensated	SOF/VEL + RBV x 12 weeks
Treatment Experienced (prior PEG/RBV)	Non-cirrhotic	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
Treatment Experienced (SOF + RBV)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
Treatment Experienced (prior NS5A-containing regimen)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks
Genotype 3		
Naïve	Non-cirrhotic	SOF/VEL X 12 weeks G/P x 8 weeks

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	Compensated cirrhosis	SOF/VEL + RBV x 12 weeks G/P x 12 weeks
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 weeks
Treatment Experienced (prior PEG/RBV only)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 16 weeks
Treatment Experienced (SOF + RBV)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks G/P x 16 weeks
Experienced (prior NS5A-containing regimen)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks
Genotype 4		
Treatment Naïve	Non-cirrhotic	SOF/VEL x 12 weeks EBV/GZR x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	SOF/VEL x 12 weeks EBV/GZR x 12 weeks G/P x 12 weeks
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 week
Treatment Experienced (prior PEG/RBV only)	Non-cirrhotic	SOF/VEL x 12 weeks EBV/GZR x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	SOF/VEL x 12 weeks EBV/GZR x 12 weeks G/P x 12 weeks
Treatment Experienced (prior NS5A-containing regimen OR sofosbuvir)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks
Genotype 5/6		
Treatment Naïve or Experienced (prior PEG-IFN/RBV only)	Non-cirrhotic or compensatedcirrhotis	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
	Decompensated cirrhosis	SOF/VEL + RBV x 12 weeks
Experienced (prior NS5A-containing regimen OR sofosbuvir)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks

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Abbreviations: CTP = Child-Turcotte-Pugh; DAA = direct acting antiviral; DCV = daclatasvir; EBV/GZR = elbasvir/grazoprevir;G/P = glecaprevir and pibrentasvir PEG = pegylated interferon;; RAV = resistance-associated variant; RBV = ribavirin; SOF = sofosbuvir; SOF/VEL = sofosbuvir/velpatasvir/voxilaprevir **No baseline NS5A RAVs. For genotype 1a patients with baseline NAS5A RAVs, extend duration to 16 weeks. ±Evidence is insufficient if the addition of RBV may benefit subjects with GT3 and cirrhosis. If RBV is not used with regimen, then baseline RAV testing should be done prior to treatment to rule out the Y93 polymorphism.
^ Rarely, genotyping assays may indicate the presence of a mixed infection (e.g., genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are limited. However, in these cases, a pangenotypic regimen is appropriate.
Ribavirin-containing regimens are absolutely contraindicated in pregnant women and in the male partners of women who are pregnant. Documented use of two forms of birth control in patients and sex partners for whom a ribavirin containing regimen is chosen is required.
Regimens other than glecaprevir/pibrentasvir (G/P;) and elbasvir/grazoprevir (EBV/GZR) should not be used in patients with severe renal impairment (GRF < 30 mL/min) or end stage renal disease requiring dialysis.
All regimens containing a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir) should not be used in patients with moderate to severe hepatic impairment (CTP B and C).

P&T Review: *9/17 (MH); 9/16; 1/16; 5/15; 3/15; 1/15; 9/14; 1/14*
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