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UNIVERSITY

Drug Use Research & Management Program

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Class Update with New Drug Evaluation: Hepatitis C

Month/Year of Review: January 2015

Generic Name: Ledipasvir and sofosbuvir

PDL Class: Hepatitis C Drugs

End date of literature search: November 2014

Brand Name (Manufacturer): Harvoni™ (Gilead Sciences)

Dossier Received: Yes

Current Status of PDL Class:

- Preferred Agents: PEGINTERFERON ALFA-2A (PEGASYS™), PEGINTERFERON ALFA-2B (PEGINTRON™), RIBAVIRIN TABLET, SIMEPREVIR (OLYSIO™), SOFOSBUVIR (SOLVALDI™)
- Non Preferred Agents: BOCEPREVIR (VICTRELIS™), RIBAVIRIN DOSE PACK (RIBIPAK™)

Research Questions:

- Is ledipasvir and sofosbuvir (LDV/SOF) more effective than currently available alternative agents for the treatment of chronic hepatitis C (CHC) in achieving a sustained virologic response (SVR) and preventing long-term complications including hepatocellular carcinoma (HCC), liver-related morbidity, and mortality?
- Is LDV/SOF safer than other available agents for the treatment of CHC genotype 1 (GT1) in adults?
- Does LDV/SOF offer improved value over currently available agents?
- What subgroups of patients will benefit most from treatment with LDV/SOF?
- Is there new comparative efficacy or safety evidence for the hepatitis C drugs relevant to make changes to current PDL and utilization management?

Conclusions:

- There is low quality evidence that 12 weeks of LDV/SOF results in high SVR12 rates among treatment-naïve (97-99%) and treatment-experienced (94-99%) adults with chronic hepatitis C virus (HCV) GT 1 infection. This is based on 2 poor quality, open-label studies with a high risk of bias.^{1,2}
- There is low quality evidence that an 8-week regimen of LDV/SOF may have similar sustained virologic response rates as a 12-week regimen of LDV/SOF in treatment-naïve adults with chronic HCV genotype 1 infection who did not have cirrhosis (94% vs. 95%; p=0.52).³
- All studies remain small, with imprecise estimates of benefits and harms, particularly in patients with cirrhosis and those 65 years and older. However, there is a large magnitude of benefit seen, and LDV/SOF appears to have potential for improved value over previously approved agents, with higher SVR rates, fewer adverse events, and increased tolerability.
- There is insufficient evidence on the relapse rates associated with LDV/SOF. Larger studies with longer follow-up are needed to adequately assess relapse rates and treatment success.
- There is insufficient to low quality evidence based on one small (n=14) nonrandomized, open-label trial that patients who have viral relapse after sofosbuvir plus ribavirin can be successfully re-treated with LDV/SOF for 12 weeks.⁴

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- There is insufficient comparative evidence evaluating direct acting antivirals. There is insufficient evidence on long-term clinical outcomes such as liver transplantation, hepatocellular carcinoma, and mortality.

Recommendations:

- Make LDV/SOF a preferred agent on the PDL.
- Implement prior authorization criteria consistent with the community standard to prioritize use so that patients defined by the AASLD guidelines as “highest priority”, who are at high risk for liver-related complications and severe extrahepatic hepatitis are treated (Appendix 1). Limit use of LDV/SOF to the following patients (highest priority based on the AASLD guidelines) at this time:
 - Stage 3 and 4 fibrosis without decompensated cirrhosis
 - Those receiving an organ transplant
 - Patients with extrahepatic manifestations, including:
 - Type 2 or 3 cryoglobulinemia with end-organ manifestations (vasculitis)
 - Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
 - Patients prescribed medication by or in consultation with a hepatologist or gastroenterologist with experience in Hepatitis C.

Reason for Update:

Since the last review of medications for Hepatitis C, there has been a new FDA drug approval (LDV/SOF), new combination approved, and new guidelines and systematic reviews released. In addition, the hepatitis C advisory committee has met again to discuss how to prioritize treatment in Oregon. This review will evaluate the new evidence available in the class.

Background:

Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma. It is also the leading indication for liver transplantation in the Western world.⁵ The goal of treatment for CHC is to prevent these long-term health complications. However, it remains difficult to design long term clinical trials that are large enough to provide direct evidence for these outcomes. The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels following completion of antiviral treatment. It is the standard marker of successful treatment in clinical trials and is associated with the long-term absence of viremia. There is some evidence of an association of achieving an SVR and reductions in mortality, liver failure, and cancer.⁵ However, this evidence is from observational studies only and those with cirrhosis prior to treatment have been shown to still be at risk for HCC during follow-up. The two major predictors of SVR are viral genotype and the pretreatment viral load. Other factors associated with an increased likelihood of achieving an SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy. Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. SVR 24 has been associated with improvements in quality of life and studies have demonstrated that SVR24 is associated with decrease in decompensated liver disease, hepatocellular carcinoma, liver transplant, and all-cause mortality. More recent studies use SVR at week 12 of follow-up (SVR12) as the primary endpoint, based on evidence that the majority of patients who have an SVR at week 12 maintain it until week 24.⁶ Relapse is defined as a patient achieving HCV RNA less than the lower limit of quantitation or the lower limit of detection at the last measurement on treatment but subsequently having a HCV RNA greater than or equal to the lower limit of quantitation or detection post treatment.⁷

Patients at greatest risk of progressing to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis (Metavir fibrosis stage 2 or greater). Patients with compensated cirrhosis are at risk of progressing to decompensation hepatocellular carcinoma, or death. The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver-related disease, and prolonging graft survival in liver transplant recipients. Disease progression varies greatly among patients with compensated liver disease and the number needed to treat to prevent long term outcomes is dependent on the baseline risk for events. The newer costly treatments with high SVR rates will have the most benefit among patients at highest risk of cirrhosis-related events.⁸

In the United States, genotype 1 infection is found in around three-quarters of patients and is associated with a lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20% of patients.⁵ Prior to 2011, the combination of pegylated interferon and ribavirin (PR) was the standard of care and only 55-60% of patients achieved a SVR. Severe adverse effects also limited the success of therapy with treatment. In 2011, the first generation direct acting antiviral protease inhibitors, boceprevir and telaprevir, were FDA approved.⁹ Several randomized controlled trials (RCTs) have showed improved SVR rates (63-79%) with triple therapy compared to pegylated interferon and ribavirin dual therapy. There is no direct comparative evidence on the effectiveness of the currently available protease inhibitors. However, these agents still come with several safety concerns and still depend on combination therapy with interferon and ribavirin which can result in serious adverse reactions. There are also important drug interactions observed with protease inhibitors.

In 2013, the second generation direct-acting antiviral agents (DAAs), simeprevir (SMV) and sofosbuvir (SOF), were approved.⁶ Sofosbuvir and ribavirin, studied together for 24 weeks in those ineligible to receive interferon, was the first and only interferon-free therapy for the treatment of genotype 1 infection. These regimens decreased the duration of therapy, decreased adverse events, and again demonstrated improved rates of SVR. However, these new drugs are expensive, and a significant challenge is identifying which patients will benefit most from receiving treatment, since only 5-20% of patients with chronic hepatitis C will develop cirrhosis over 20 years.¹⁰ In addition, recent data from show real world discontinuation rates of SOF + PR may be up to 5-times greater than rates seen in clinical trials. In 2014, several additional interferon-free therapies that combine two or more DAAs have been studied, including LDV/SOF.

Methods:

A Medline literature search ending December 1, 2014 for new systematic reviews and RCTs comparing LDV/SOF to placebo or other treatments of hepatitis C was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, systematic reviews¹⁰, two clinical guidelines^{11,12}, and three phase 3 trials¹⁻³ evaluating LDV/SOF were identified.

Systematic Reviews:

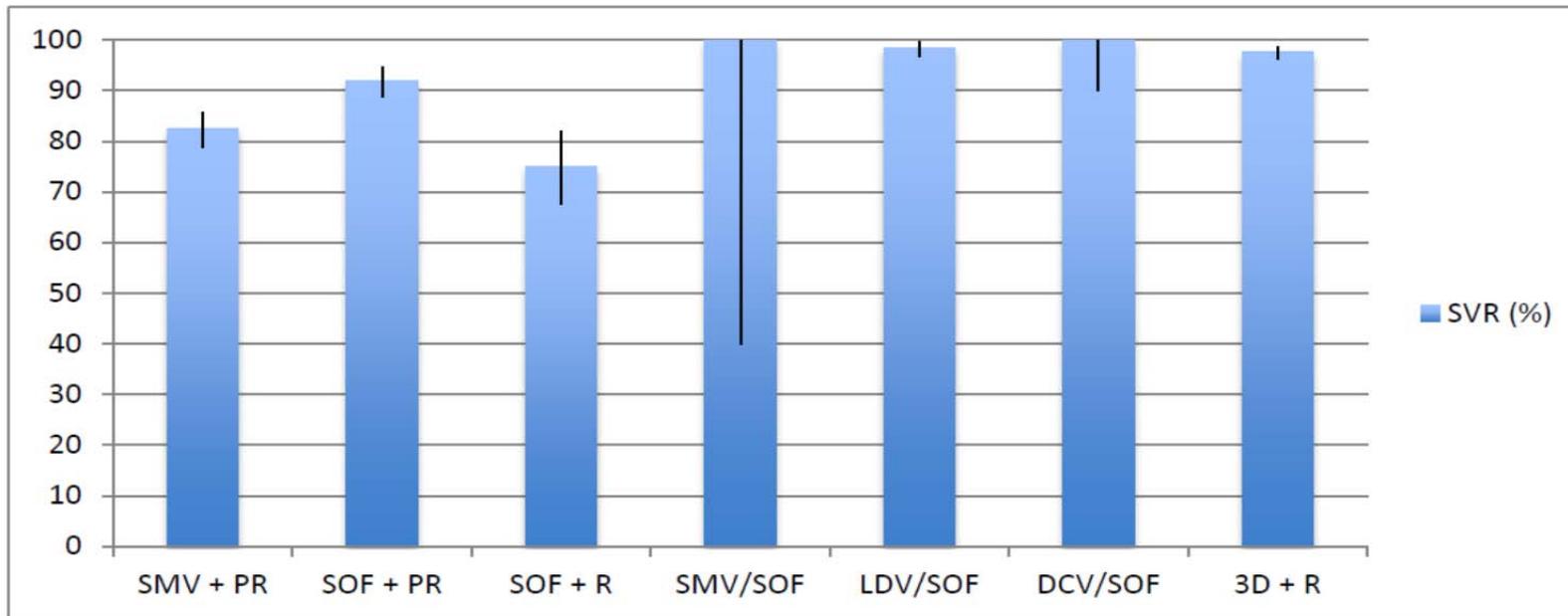
Institute for Clinical and Economic Review (ICER)

ICER released a draft report comparing the clinical effectiveness and value of therapies for the treatment of patients with GT1 CHC infection for deliberation and voting at the next public meeting of the California Technology Assessment Forum (CTAF).¹⁰ Therapies included in the assessment were simeprevir, sofosbuvir, the combination of simeprevir and sofosbuvir, LDV/SOF, daclatasvir + sofosbuvir (not yet FDA approved), and paritaprevir + ritonavir + ombitasvir + dasabuvir (not yet FDA approved). The authors noted limited head to head trials and issues with selection bias. Because there are no randomized trials, it was not possible

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to perform a network meta-analysis. A summary of SVR12 rates with each combination was provided and a meta-analysis of proportions was used to combine them. Results were estimated in four subgroups of patients: treatment naïve with and without cirrhosis, and treatment experienced with and without cirrhosis. Meeting abstracts, FDA documents, and press releases were used as sources. The authors concluded that high-quality observational data from real-world settings will be essential to evaluate the comparative effectiveness of the combination of DAA agents to see if the high SVR rates are also seen in real practice settings. SVR and 95% Confidence Intervals for the various regimens in treatment-naïve non-cirrhotic patients are included in the following figure:

Figure 1: SVR12 in treatment-naïve non-cirrhotic

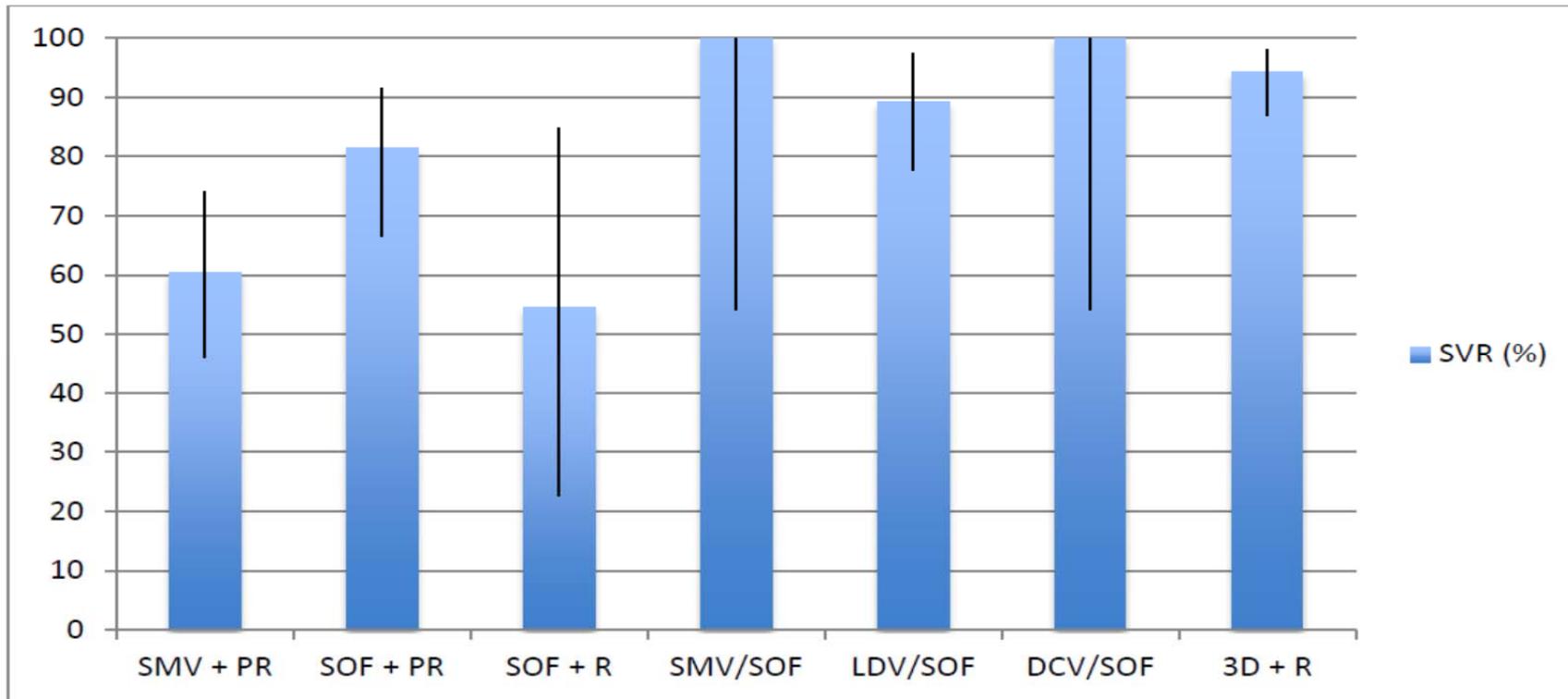


Abbreviations: SMV: simeprevir, PR: pegylated interferon and ribavirin, SOF: sofosbuvir, R: ribavirin, LDV: ledipasvir, DCV: daclatasvir, 3D: paritaprevir + ritonavir + ombitasvir + dasabuvir

The highest rates of SVR were seen with SMV/SOF and LDV/SOF; however, the wide confidence interval with the SMV/SOF regimen is because it has only been studied in 6 patients with SVR rates ranging from 39-100%. Discontinuation rates ranged from 0 to 10% in treatment-naïve patients. Regimens containing ribavirin had the highest discontinuation rates.

There are no direct comparisons of any of the DAA regimens. Trends suggest that DAA combinations appear to have higher SVR rates than single DAA + R or PR. However, there is less certainty for treatments in patients with cirrhosis, as seen in the figure below.

Figure 2: SVR rates in treatment naive and cirrhosis



Abbreviations: SMV: simeprevir, PR: pegylated interferon and ribavirin, SOF: sofosbuvir, R: ribavirin, LDV: ledipasvir, DCV: daclatasvir, 3D: paritaprevir + ritonavir + ombitasvir + dasabuvir

The authors concluded the following:

- There is moderate certainty of substantial net benefit and high certainty of at least a small benefit with the four new multiple DAA therapies compared to the older single DAA-based regimens of SMV or SOF based on shorter duration of therapy, fewer side effects, and less burdensome treatment. The limitations are the small study sizes with no relevant comparators and SVR 12 being only a moderately validated intermediate outcome.
- There is low certainty of superiority of any of the multiple DAA therapies compared to each other, as there are no head to head studies.

New Guidelines:

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

In October 2014, CADTH released recommendations for DAA agents for CHC GT1.¹³ Evidence informed recommendations were developed by the Canadian Drug Expert Committee. The summary of recommendations are as followed:

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

American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA):

The AASLD/IDSA guidelines prioritize patients for treatment and give the highest priority for those patients with advanced fibrosis (Metavir F3), those with compensated cirrhosis (Metavir F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C.¹⁴ They go on to state that: “Based on available resources”, treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis complications are given higher priority. These patient groups are described below.

Highest Priority for Treatment	
	Strength and level of evidence
Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)	Class I, Level A
Organ transplant	Class I, Level B
Type 2 or 3 cryoglobulinemia with end-organ manifestations (vasculitis)	Class I, Level B
Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis	Class IIa, Level B
High Priority for Treatment	
Fibrosis (Metavir F2)	Class I, Level B
HIV-1 coinfection	Class I, Level B
Hepatitis B virus coinfection	Class IIa, Level C
Other coexistent liver disease	Class IIa, Level C
Debilitating fatigue	Class IIa, Level B
Type 2 Diabetes Mellitus	Class IIa, Level B
Porphyria cutanea tarda	Class IIb, Level C

LDV/SOF is not included for consideration in the guidelines.

New Safety Alerts:

None

New Formulations or Indications:

The FDA approved the combination of SMV/SOF as an interferon-free treatment option for GT1 CHC infection. The data for the FDA approval comes from the COSMOS study, which was reviewed previously.¹⁵ This is the only published trial that evaluated the combination of SMV/SOF and only included 81 treatment-experienced patients with GT1 fibrosis stages F0 to F2 (Cohort 1) and 87 patients with fibrosis stages F3 or F4 (Cohort 2). Overall, the SVR12 was 92% (154/168). The quality of these data is poor as the study was open-label without a control group, and the number of patients was small, leading to imprecise SVR estimates.

New Drug Evaluation:*FDA approved indications:*

Ledipasvir and sofosbuvir (LDV/SOF) (Harvoni™) is a fixed dose combination of ledipasvir, a HCV NS5A inhibitor, and sofosbuvir, a HCV nucleotide analog NS5B polymerase inhibitor, indicated for the treatment of CHC GT1 infection in adults.¹⁶

Clinical Efficacy Data:

There are five phase 2 studies and three phase 3 studies evaluating LDV/SOF.¹⁷ Phase 2 studies demonstrated that LDV/SOF is effective in achieving SVR among previously untreated patients with HCV GT1 infection, including those with compensated cirrhosis.^{18,19} FDA approval was based on three primary phase 3 randomized studies with similar design in patients with GT1 (ION 1-3). These are described in the evidence table below. There was no control group in any of the trials and all were open-label, increasing the risk of bias. The primary endpoint in each study was SVR12 and the objective was that each treatment arm was superior to a historical control rate. ION-1 and ION-3 trials were conducted in treatment-naïve patients and ION-2 was conducted in patients who had previously failed an interferon regimen including those who may have failed a protease inhibitor (telaprevir or boceprevir) regimen. All of the trials had significant exclusion criteria that limits the generalizability of results to the real world population and reduces external validity. This included those with decompensated cirrhosis, clinically relevant drug abuse within 12 months, alcohol misuse, hepatitis B virus (HBV), HIV infection, significant pulmonary or cardiac disease, and prior discontinuation of treatment due to an adverse event.

ION-1 was a poor quality study in previously untreated patients with GT 1 CHC.² Patients were randomized to 12 or 24 weeks of LDV/SOF treatment with or without ribavirin. Risk of bias is high in the trial as there was no comparator group and it was not blinded. SVR was compared with an adjusted historical rate of 60% that was based on SVR rates in trials of telaprevir and boceprevir. During treatment, 2 people had virological relapse. Subgroup analysis demonstrated similar rates of SVR12. In patients with cirrhosis, SVR ranged from 94 to 100%, 97 to 99% with genotype 1a infection, and 91 to 100% in black patients. However, the confidence intervals were much wider for the following subgroups: interferon ineligible patients, those 65 years of age or older, and patients with cirrhosis. The authors concluded that no additional benefit appeared to be associated with the addition of ribavirin or with extension of the duration of treatment to 24 weeks.

ION-2 was a poor quality study that included patients previously treated who were either non-responders or relapsers.¹ About half of the participants had prior treatment with a protease-inhibitor regimen, while the remaining received interferon and ribavirin dual therapy. A total of 20% of patients had cirrhosis, but

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patients were excluded if they had decompensated cirrhosis. Like ION-1, patients were randomized to 12 or 24 weeks of LDV/SOF treatment with or without ribavirin. All four treatment groups were compared to a historical response rate of 25%. Overall, results were similar in the 12-week regimens compared to 24 weeks (94-99%). However, studies were not powered to compare responses to regimens with and without ribavirin or to 12 weeks versus 24 weeks of treatment. The addition of ribavirin did not seem to significantly increase SVR12 rates and was associated with greater treatment related adverse events. In the subgroup of patients with cirrhosis, SVR12 rates were 81.8% and 86.4% in the 12-week regimen groups compared to 100% in the 24-week regimen groups, including both with and without ribavirin. The study was not powered for intergroup comparisons. Eleven patients (2%) had a virologic relapse after treatment, all of which received 12 weeks of treatment. Rates were similar among those who had previously received peginterferon and ribavirin and in those who had a protease-inhibitor regimen. Six of the 11 patients (55%) who relapsed had detectable NS5A-resistant variants at baseline, and all 11 had detectable variants at the time of relapse. Subgroup analyses showed much wider confidence intervals around SVR rates for those 65 years of age and older and in those with cirrhosis. A regression analysis identified the absence of cirrhosis as the only baseline factor associated with a significant increase in rate of response.

ION-3 was a poor quality trial comparing 12-week SVR rates between an 8-week regimen of LDV/SOF with or without ribavirin to a 12-week regimen of LDV/SOF without ribavirin in patients with CHC without cirrhosis.³ A secondary endpoint was the noninferiority of 8 weeks of LDV/SOF to 12 weeks of treatment measured by SVR12 using a noninferiority margin of 12 percentage points. The SVR rate in the 8-week LDV/SOF treatment group was noninferior to the other two treatment groups (LDV/SOF + ribavirin x 8 weeks and LDV/SOF x 12 weeks). However, 12% is a high margin from a clinical perspective.²⁰ Subgroup analysis showed slightly lower SVR rates in those 65 years of age and older treated with LDV/SOF for 8 weeks (89.5% [95% CI 66.9 to 98.7%]) and in interferon ineligible patients treated with LDV/SOF for 8 weeks (92.3% [95% CI 88.1 to 96.3%]). In all three treatment groups, the confidence intervals were wider in these two subgroups. Fibrosis score (F0-F3) did not seem to impact SVR rates in any of the treatment groups. Overall, 23 patients had a virologic relapse after therapy, including 11 (5%) in the group that received 8 weeks of LDV/SOF, 9 (4%) in the group that received 8 weeks of therapy with ribavirin, and 3 (1%) in the 12-week group. The difference in relapse rates between the combined 8 week arms and the 12 week arm was 3.3% (95% CI 0.2 to 6.0%).¹⁷ Therefore, the FDA recommends that a treatment duration of 8 weeks can only be considered in patients with more favorable baseline characteristics, including treatment-naïve patients without cirrhosis who have a pre-treatment HCV RNA less than 6 million IU/mL.¹⁷

Subgroup Populations:

The LDV/SOF regimen was evaluated in patients with chronic HCV GT 1 that relapsed after SOF plus ribavirin therapy in a small, nonrandomized poor quality phase 2a open-label study.⁴ Patients who had relapse after 24 weeks of treatment with SOF plus ribavirin were offered re-treatment with LDV/SOF (n=14) for 12 weeks. The primary end point was the proportion of patients with unquantifiable plasma HCV load 12 weeks after treatment completion in an intention-to-treat (ITT) analysis. Most patients were black men with an unfavorable interleukin-28B non-CC genotype. All patients (100%) achieved SVR12 after completion of treatment and had HCV RNA levels below the lower limit. All patients completed treatment and no serious adverse events occurred. The most common were myalgia and hypophosphatemia. Results of this study should be interpreted with caution, as it was extremely small (n=14) with a high risk of selection and performance bias.

One phase 2 unpublished study (ELECTRON) explored the safety and tolerability of treatment-naïve patients with CHC genotype 2 and genotype 3. These subjects had an 80% SVR12 (8/10 patients) with a 95% CI of 44.4-97.5%. The two failures who both relapsed had HCV GT3a infection. The FDA reviewer commented that available efficacy data in HCV GT3 patients are limited and are not considered sufficient for a labeling conclusion at this time.¹⁷

An ongoing trial is evaluating LDV/SOF for 24 weeks in patients who did not have a response to an 8 or 12-week regimen of LDV/SOF.

Clinical Safety:

In clinical trials, the overall percentage of serious adverse events and discontinuations due to adverse events was low (0%, <1% and 1% for those receiving 8, 12, and 24 weeks, respectively).¹⁶ The most common adverse events were fatigue, headache, insomnia, and nausea. Rates of adverse events were higher in the groups treated for 24 weeks than 12 weeks, and in those treated with ribavirin than in the groups that did not. Patients in the groups that received ribavirin had higher rates of events known to be associated with ribavirin therapy (fatigue, nausea, insomnia, arthralgia, cough, rash, irritability, dyspnea, and anemia). Overall, rates of adverse events were lower in the group receiving 12 weeks of LDV/SOF without ribavirin compared to the other three treatment groups. Larger trials of longer duration, including patients more likely to be seen in clinical practice, are needed to fully assess the safety risks associated with treatment of LDV/SOF.

There were a total of 37 virologic failures from phase 3 trials; 35 from relapse. Overall, 63% of the failures had NS5a resistance substitution. There was a 3.6% relapse rates in those with one baseline NS5A polymorphism. Relapse rates were higher (9.5%) in patients with at least 2 baseline NS5A resistance-associated polymorphisms.¹⁷ The FDA reviewer states that issues of optimal retreatment duration, contribution of ribavirin and impact on the number of certain types of NS5A resistance substitutions remain unclear at this time.¹⁷

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

- 1) Hepatocellular Carcinoma
- 2) Mortality
- 3) Liver Transplant
- 4) Discontinuation Rates Due to Adverse Events

Primary Study Endpoint:

- 1) Sustained Virologic Response at week 12 after the end of treatment (SVR12)

<p>ION-2¹ (previously treated)</p> <p>Open-label, randomized</p>	<p>Ledipasvir 90mg/sofosbuvir 400mg +/- ribavirin:</p> <p>1) 12 weeks 2) 12 weeks (+ rib) 3) 24 weeks 4) 24 weeks (+rib)</p>	<p>Prior virologic failure; chronic HCV GT1 infection 20% with cirrhosis 52% had prior treatment with a protease-inhibitor 18% black Mean age: 56</p> <p><u>Inclusion Criteria:</u> Virologic failure (non-responder or relapse), Lab parameters WNL (ALT/AST, Hgb, platelets, INR, albumin, bilirubin, HgA1C, CrCl), normal ECG, HCV treatment naïve</p> <p><u>Exclusions Criteria:</u> Clinically relevant drug abuse within 12 mo, clinically-significant illness that may interfere with compliance and treatment, alcohol misuse, HBV, or HIV infection, hepatic decompensation, significant pulmonary or cardiac disease, psychiatric hospitalization, discontinued prior treatment due to an adverse event</p>	<p>440</p> <p>1) 109 2) 111 3) 109 4) 111</p>	<p><u>SVR12:</u> 1) 102 (94%; 95% CI 87-97) 2) 107 (96%; 95% CI 91-99) 3) 108 (99%; 95% CI 95-100) 4) 110 (99%; 95% CI 95-100)</p> <p>Compared to historical rate of 25%: p<0.001 for all comparisons</p>	<p>N/A</p>	<p><u>Discontinuations due to Adverse Events:</u> 0</p> <p><u>Serious AE:</u> 1) 0 (0%) 2) 0 (0%) 3) 6 (6%) 4) 3 (3%)</p> <p><u>Relapse:</u> 1) 7 (6.5%) 2) 4 (3.6%) 3) 0 (0%) 4) 0 (0%)</p>	<p>N/A</p>	<p>Quality Rating: Poor</p> <p>Internal Validity: <u>Selection:</u> Interactive Web and Voice Response System used for randomization and treatment assignment; higher percentage of non-white participants in group 1; higher percentage of previous protease-inhibitor regimen in 12 –week groups <u>Performance:</u> High RoB; open label ; compared to historical rate; no control. <u>Detection:</u> open label; objective outcome <u>Attrition:</u> Low RoB; low overall attrition (<1%) and similar between groups</p> <p>Applicability: <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Significant inclusion and exclusion criteria decrease generalizability to hepatitis C population <u>Setting:</u> 64 sites in US <u>Outcomes:</u> No long term clinical outcomes evaluated. SVR 24 data not included. Some evidence that SVR 24 is associated with improved clinical outcomes.</p> <p>No comparator group; SVR was compared with an adjusted historical rate of 25%</p>
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ION-3 ³ Open-label; randomized	Ledipasvir 90mg/ sofosbuvir 400mg +/- ribavirin: 1) 8 weeks 2) 8 weeks (+ rib) 3) 12 weeks	Previously untreated patients without cirrhosis; chronic HCV GT1 infection 19% black Mean age: 52 56% F0-F2 94% interferon eligible <u>Inclusion Criteria:</u> treatment naïve, absence of cirrhosis, Lab parameters WNL (ALT/AST, HgB, platelets, INR, albumin, bilirubin, HGA1C, CrCl), normal ECG, HCV treatment-naïve <u>Exclusions Criteria:</u> Cirrhosis clinically relevant drug abuse within 12 mo, clinically-significant illness that may interfere with compliance and treatment, alcohol misuse, HBV, or HIV infection, hepatic decompensation, significant pulmonary or cardiac disease, psychiatric hospitalization, discontinued prior treatment due to an adverse event	647 1) 215 2) 216 3) 216	<u>SVR12:</u> 1) 202 (94%; 95% CI 90-97) 2) 201 (93%; 95% CI 89-96) 3) 206 (95%; 95% CI 92-98) Compared to historical rate of 60%: p<0.001 for all comparisons Differences in Proportions (Noninferiority)*: 1 vs. 3: -1.4% (-6.4 to 3.6); p=0.52 1 vs. 2: 0.9% (-3.9 to 5.7); p=0.70 *Prespecified noninferiority margin was -12 percentage points	N/A	<u>Discontinuations due to Adverse Events:</u> 3 (<1%) <u>Serious AE:</u> 1) 4 (2%) 2) 1 (<1%) 3) 5 (2%) <u>Relapse:</u> 1) 11 (5.1%) 2) 9 (4.2%) 3) 3 (1.4%)	N/A	Quality Rating: Poor Internal Validity: <u>Selection:</u> Interactive Web and Voice Response System used for randomization and treatment assignment; <u>Performance:</u> High RoB; open label ; compared to historical rate; no control. <u>Detection:</u> open label; objective outcome <u>Attrition:</u> Low RoB; low overall attrition (2%) Higher in the LDV/SOF x 12 week group (3.2%) Applicability: <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Significant inclusion and exclusion criteria decrease generalizability to hepatitis C population <u>Setting:</u> 58 sites in US <u>Outcomes:</u> No long term clinical outcomes evaluated. SVR 24 data not included. Some evidence that SVR 24 is associated with improved clinical outcomes. Nonclinical, no comparator group; SVR was compared with an adjusted historical rate of 60%
Abbreviations: ALT: alanine aminotransferase, ARI: absolute risk increase, ARR: absolute risk reduction, AST: aspartate aminotransferase, CI: confidence interval, CrCl: Creatinine Clearance, GT1: genotype 1, HBV: hepatitis B virus, HCV: hepatitis C virus, Hgb: hemoglobin, INR: international normalized ratio, SVR12: sustained virologic response 12 weeks after completion of treatment, RoB: risk of bias, NNH: number needed to harm, NNT: number needed to treat, rib: ribavirin, WNL: within normal limits								

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

Harvoni is a fixed-dose combination of ledipasvir and sofosbuvir, which are direct-acting antiviral agents against the hepatitis C virus. Ledipasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication. Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. Sofosbuvir is a prodrug that undergoes intracellular metabolism to the pharmacologically active uridine analog triphosphate (GS-461203), which acts as a chain terminator.

PHARMACOKINETICS¹

Parameter	Result
Oral Bioavailability	Not reported
Protein Binding	Ledipasvir: >99.8% bound Sofosbuvir: 61-65% protein bound
Elimination	Ledipasvir: 86% eliminated unchanged in feces Sofosbuvir: Renal clearance is major pathway; 80% excreted unchanged in urine, 14% feces
Half-Life	Ledipasvir: 47 hours Sofosbuvir: 27 hours (metabolite)
Metabolism	Ledipasvir: Non-CYP mediated pathways; oxidative metabolism via an unknown mechanism Sofosbuvir: Non-CYP mediated pathways in the liver involving

DOSE & AVAILABILITY¹

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
90 mg ledipasvir and 400 mg sofosbuvir	Oral	One tablet once daily with or without food.	No dose adjustments recommended in mild or moderate renal impairment or hepatic impairment. The safety and efficacy has not been established in patients with severe renal impairment (GFR < 30ml/min/1.73m ²) or ESRD requiring hemodialysis or in decompensated cirrhosis.	No dose adjustments recommended	Not established in decompensated cirrhosis	Not established	No dose adjustment	Recommended Treatment Duration: <ul style="list-style-type: none"> • Treatment-naïve with or without cirrhosis: 12 weeks • Treatment-experienced without cirrhosis: 12 weeks • Treatment-experienced with cirrhosis: 24 weeks • Treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL: 8 weeks can be considered

DRUG SAFETY¹*Pregnancy/Lactation:*

Pregnancy Category B: There are no adequate and well controlled trials in pregnant women. LDV/SOF should be used during pregnancy only if the potential benefit justified the potential risk to the fetus.

Lactation: Unknown if drug is present in human breast milk.

Serious (REMS, Black Box Warnings, Contraindications):

REMS: N/A

Black Box Warning: None

Contraindications: None

Warnings and Precautions:

Risk of Reduced Therapeutic Effect Due to P-gp Inducers: The concomitant use of LDV/SOF and P-gp inducers (rifampin, St. John's wort) may significantly decrease ledipasvir and sofosbuvir plasma concentrations and lead to a reduced therapeutic effect.

Drug Interactions:

The following table provides a list of established or potentially clinically significant drug interactions.¹⁶

Concomitant Drug Class: Drug Name	Effect on Concentration^b	Clinical Comment
Acid Reducing Agents:	↓ ledipasvir	Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir.
Antacids (e.g., aluminum and magnesium hydroxide)		It is recommended to separate antacid and HARVONI administration by 4 hours.
H ₂ -receptor antagonists ^c (e.g., famotidine)		H ₂ -receptor antagonists may be administered simultaneously with or 12 hours apart from HARVONI at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors ^c (e.g., omeprazole)		Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions.
Antiarrhythmics: digoxin	↑ digoxin	Coadministration of HARVONI with digoxin may increase the concentration of digoxin. Therapeutic concentration monitoring of digoxin is recommended when coadministered with HARVONI.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007	Coadministration of HARVONI with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin ^c rifapentine	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007	Coadministration of HARVONI with rifabutin or rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended. Coadministration of HARVONI with rifampin, a P-gp inducer, is not recommended [<i>see Warnings and Precautions (5.1)</i>].
HIV Antiretrovirals:		

efavirenz, emtricitabine, tenofovir disoproxil fumarate (DF)	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving HARVONI concomitantly with the combination of efavirenz, emtricitabine and tenofovir DF. Refer to VIREAD, TRUVADA, or ATRIPLA prescribing information for recommendations on renal monitoring.
Regimens containing tenofovir DF and a HIV protease inhibitor/ritonavir <ul style="list-style-type: none"> • atazanavir/ritonavir + emtricitabine/tenofovir DF^c • darunavir/ritonavir + emtricitabine/tenofovir DF^c • lopinavir/ritonavir + emtricitabine/tenofovir DF 	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of HARVONI and a HIV protease inhibitor/ritonavir has not been established. Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for recommendations on renal monitoring.
elvitegravir, cobicistat, emtricitabine, tenofovir DF	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of HARVONI and the combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF has not been established. Coadministration is not recommended.
tipranavir/ritonavir	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007	Coadministration of HARVONI with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
HCV Products: simeprevir ^c	↑ ledipasvir ↑ simeprevir	Concentrations of ledipasvir and simeprevir are increased when simeprevir is coadministered with ledipasvir. Coadministration of HARVONI with simeprevir is not recommended.
Herbal Supplements: St. John's wort (<i>Hypericum perforatum</i>)	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007	Coadministration of HARVONI with St. John's wort, a P-gp inducer is not recommended [see <i>Warnings and Precautions (5.1)</i>].
HMG-CoA Reductase Inhibitors: rosuvastatin	↑ rosuvastatin	Coadministration of HARVONI with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Coadministration of HARVONI with rosuvastatin is not recommended.

Appendix 2: Proposed PA Criteria:

Hepatitis C Direct-Acting Antivirals

Goal(s):

- Approve cost effective treatments of chronic hepatitis C which are supported by the medical literature when there is available evidence.
- Treat the patient population in greatest need of treatment and who will benefit the most from therapy.
- Provide consistent patient evaluations across all hepatitis C treatments.

Length of Authorization:

- 8-12 weeks

Requires PA:

- All drug regimens in the Hepatitis C PDL Class

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

Approval Criteria		
<p>5. Is the medication being prescribed by or in consultation with a hepatologist or gastroenterologist with experience in Hepatitis C?</p>	<p>Yes: Go to #6.</p>	<p>No: Pass to RPh; deny for appropriateness.</p> <p>Forward to DMAP for further review to determine appropriateness of prescriber.</p>
<p>6. Does the patient have a biopsy or other non-invasive technology (Fibroscan), including serum tests (Fibrosure, Fibrotest) to indicate Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4) OR radiologic, laboratory, or clinical evidence of cirrhosis without ongoing progressive decompensation (MELD score between 8 and 11), and expected survival from non-HCV associated morbidity should be greater than 5 years?</p>	<p>Yes: Go to #7.</p>	<p>No: Go to #8.</p> <p>Note: Patients with a MELD score >11 may be eligible for therapy, but only after review by the DMAP medical director.</p> <p>Forward fee-for-service cases to DMAP for Medical Director Review and notify requesting provider of pending review.</p>
<p>7. Does the patient have decompensated cirrhosis?</p>	<p>Yes: Pass to RPh; deny for appropriateness</p>	<p>No: Go to #10</p>
<p>8. Does the patient have one of the following extrahepatic manifestations of hepatitis C and who have formal documentation from a relevant specialist that their condition is HCV related, and expected survival from non-HCV associated morbidity should be greater than 5 years?</p> <ul style="list-style-type: none"> a. Type 2 or 3 cryoglobulinemia with end-organ manifestations (vasculitis) b. Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis 	<p>Yes: Go to #10.</p>	<p>No: Go to #9.</p>

Approval Criteria		
<p>9. Does the patient have Hepatitis C Virus in the transplant setting, including the following scenarios:</p> <ul style="list-style-type: none"> a) Patient is listed for a transplant and it is essential to prevent recurrent hepatitis C infection post-transplant b) Post-transplant patients with Stage 4 fibrosis c) Post-transplant patients with fibrosing cholestatic hepatitis due to HCV infection <p>And expected survival from non-HCV associated morbidity should be greater than 5 years?</p>	<p>Yes: Go to #10.</p> <p>Note: Patients in the transplant setting may be eligible for therapy, but only after review by the DMAP Medical Director.</p> <p>Forward case to DMAP for Medical Director Review and notify requesting provider of pending review.</p>	<p>No: Pass to RPh; deny for medical appropriateness.</p> <p>Note: Other scenarios not included can be brought to the Medical Director on a case by case basis.</p>
<p>10. Has the patient been abstinent from IV drug, illicit drugs and marijuana use, AND alcohol abuse for ≥ 6 months? AND If the patient has a history of alcohol abuse, has the patient been abstinent from alcohol use for ≥ 6 months?</p>	<p>Yes: Go to #11.</p>	<p>No: Pass to RPh; deny for appropriateness.</p>
<p>11. Does the patient have significant renal impairment (CrCl , 30 ml/min) or end state renal disease (ESRD)?:</p>	<p>Yes: Pass to RPh; deny for appropriateness.</p>	<p>No: Go to #12.</p>
<p>12. Does the patient have a baseline HCV RNA level?</p>	<p>Yes: Record value and go to #13.</p>	<p>No: Pass to RPH. Request provider obtains baseline lab value.</p>
<p>13. What Hepatitis C genotype is the patient? Record Genotype:</p>	<p>Record Genotype and go to #14.</p>	
<p>14. Is the prescribed drug ledipasvir/sofosbuvir (Harvoni®) and is the regimen and duration appropriate for patient genotype based on the dosing and administration table below?</p>	<p>Yes: Approve for 8-12 weeks based on dosing and administration table.</p>	<p>No: Go to #15</p>
<p>15. Is the prescribed drug sofosbuvir (Solvaldi®)?</p>	<p>Yes: Go to #16</p>	<p>No: Pass to RPh; deny for appropriateness.</p>

Approval Criteria

16. Does the patient have Genotype 2 hepatitis C infection?

Yes: Approve for 12 weeks based on dosing and administration table below

No: Pass to RPh; deny for appropriateness. Encourage prescriber to use ledipasvir/sofosbuvir (Harvoni) for other genotypes (see table below).

Dosage and Administration:

Genotype 1			
Naïve	Without Cirrhosis and HCV RNA < 6 million IU/ml	LDV/SOF 1 tablet QD	8 weeks
	Without Cirrhosis and HCV RNA ≥ 6 million IU/ml	LDV/SOF 1 tablet QD	12 weeks
	With Cirrhosis	LDV/SOF 1 tablet QD	12 weeks
Experienced	Without Cirrhosis	LDV/SOF 1 tablet QD	12 weeks
	With Cirrhosis	LDV/SOF 1 tablet QD + RBV	12 weeks
Genotype 2			
Naïve and Experienced	With or Without Cirrhosis	SOF 400 mg + RBV	12 weeks*
Genotype 3			
Naïve or Experienced	With or Without Cirrhosis	LDV/SOF 1 tablet QD + RBV SOF 400 mg + RBV	12 weeks 24 weeks
Genotype 4 and 6			
Naïve or Experienced	With or Without Cirrhosis	LDV/SOF 1 tablet QD	12 weeks
*Previous nonresponders to PEG/RBV with cirrhosis may benefit by extension of therapy to 16 weeks			
Abbreviations: LDV/SOF: Ledipasvir and sofosbuvir (Harvoni®); RBV: ribavirin; SOF: sofosbuvir (Sovaldi®)			

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