Class Update with New Drug Evaluation: Direct Antivirals for Hepatitis C

Date of Review: January 2016
Generic Name: daclatasvir
Generic Name: ombitasvir/paritaprevir/ritonavir

Current Status of PDL Class:
See Appendix 1.

Purpose for Class Update:
Since the last P&T review of Hepatitis C there have been two new drug approvals, updated guidelines, new FDA approved indications, and a new safety alert. The new comparative evidence for the class will be reviewed here.

Research Questions:
1. Is ombitasvir/paritaprevir/ritonavir (OMB/PTV-R) 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?
2. Is OMB/PTV-R safer than other available agents for the treatment of CHC in adults?
3. What subgroups of patients will benefit most from treatment with OMB/PTV-R?
4. Is daclatasvir in combination with sofosbuvir (DCV/SOF) more effective than currently available agents for the treatment of CHC in achieving a SVR and preventing long-term complications?
5. Is DCV/SOF safer than other available agents for the treatment of CHC in adults?
6. What subgroups of patients will benefit most from treatment with DCV/SOF?

Conclusions:
• There is low quality evidence from one phase 3 trial (ALLY-3), with significant methodological flaws and a high magnitude of effect, that DCV/SOF achieved an SVR of 89% in subjects with genotype 3 (GT3) CHC. However, SVR rates were reduced in hepatitis C virus (HCV) genotype 3 (GT3) patients with cirrhosis (63%) compared to those without cirrhosis (96%). As a result, the optimal duration of HCV GT3 patients with cirrhosis has not been established. However, there are not other treatment options available that are more effective in this population. Alternative regimens for the treatment of GT3 patients includes SOF + ribavirin (RBV) for 24 weeks which was shown to result in lower SVR rates or the off-label use of LDV/SOF + RBV for 12 weeks based on the limited ELECTRON trial.23
• There is low quality to insufficient evidence that DCV/SOF is efficacious in GT 1, 2, and 3 CHC and insufficient data in patients with cirrhosis and these genotypes.4,5
• There is low quality evidence from one phase 2b trial (PEARL-1), with significant methodological flaws, that OMB/PTV-R achieved an SVR of 91-100% in GT4 CHC without cirrhosis.6
• There is insufficient evidence that OMB/PTV-R is efficacious in patients with cirrhosis and no data on patients with non-GT4 CHC or in treatment experienced patients with regimens other than pegylated interferon/ribavirin.
• 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:
• Include DCV/SOF in current PA criteria as a treatment option for patients with GT3 CHC.
• Include OMB/PTV-R + RBV as a treatment option for patients with GT4 CHC without cirrhosis.
• Evaluate comparative costs for preferred drug list (PDL) status.

Previous Conclusions:
• There is low quality evidence 12 weeks of ledipasvir/sofosbuvir (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.
• 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-naive adults with chronic HCV genotype 1 infection who did not have cirrhosis (94% vs. 95%; p=0.52).
• 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 SOF plus ribavirin can be successfully re-treated with LDV/SOF for 12 weeks.
• 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.

Previous 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” at high risk for liver-related complications and severe extrahepatic hepatitis are treated. 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.

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. 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, as measured by a sensitive polymerase chain reaction assay. It is the standard mark 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. However, this evidence is from observational studies only and those with cirrhosis prior to treatment have been shown to still be at risk for hepatocellular carcinoma (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 a decrease in compensated 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. 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. In addition, genetic variation in both virus and host can affect treatment response.

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. However, a recent cost effectiveness study found that treating HCV infection at early stages of fibrosis appears to improve health outcomes and to be cost-effective but incurs substantial costs.

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. Genotype 1 includes subgenotypes, of which 1a and 1b are the most common. Cure rates for genotype 1a and 1b infection may differ depending on the treatment regimen. Therapies to treat HCV infection have advanced significantly over the past several years. Prior to 2011, the combination of pegylated interferon and ribavirin (PEG/RBV) was the standard of care and approximately 55-60% of patients achieved a SVR. Severe adverse effects also limited the success of therapy. In 2011, the first generation direct acting antiviral protease inhibitors, boceprevir and telaprevir, were FDA approved. Several randomized controlled trials (RCTs) showed improved SVR rates (63-79%) with triple therapy compared to PEG/RBV dual therapy. However, these agents still come with several safety concerns and still depend on combination therapy with PEG/RBV which can result in serious adverse reactions. With the recent development of interferon-free regimens, these therapies have gone out of favor.

Author: Herink
Date: January 2016
In 2013, the second-generation direct-acting antiviral agents (DAAs), simeprevir (SMV) and sofosbuvir (SOF) were approved. Sofosbuvir and RBV, studied together for 24 weeks in those ineligible to receive interferon, was the first 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. In addition, recent data from show real world discontinuation rates of SOF + PEG/RBV may be up to 5-times greater than rates seen in clinical trials. In late 2014, two additional interferon-free therapies that combine two or more DAAs have been studied, including LDV/SOF and the OMB/PTV-R + DAS regimen. 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. Technivie is a fixed dose combination including ombitasvir, a hepatitis C virus NS5A inhibitor; paritaprevir, a hepatitis C virus NS3/4A protease inhibitor; and ritonavir, a potent CYP3A inhibitor that is not active against HCV but boosts concentrations of paritaprevir. It was FDA approved for use in combination with ribavirin in patients without cirrhosis and with genotype 3 CHC. Treatment options for patients with genotype 3 remain limited and have required a longer duration of therapy (24 weeks) and the addition of ribavirin. Daclatasvir is a NS5A inhibitor approved for use in combination with sofosbuvir (DCV/SOF) for patients with genotype 3 CHC.

Studies including patients with decompensated cirrhosis, renal failure, or other comorbidities and minority racial and ethnic groups are lacking and these remain some of the most difficult patients to treat.

**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. The Medline search strategy used for this review is available in Appendix 4, which includes dates, 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.

**New Guidelines:**
The guidelines from the American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) are routinely updated to reflect the rapidly changing drug class. Current guidelines recommend treatment for all patients; expect those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. However, the guidelines have many limitations and the overall methodological quality of the guidance was poor. The panel lacked non-specialist members and there was no assessment of risk of bias for individual studies. The authors and sponsors of the guidance had multiple conflicts of interest. The following recommendations for initial treatment of HCV infection are provided:

1. Treatment-naive patients with HCV genotype 1a infection
   a. DCV/SOF for 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV
      Rating: Class I, Level B (no cirrhosis); Class IIa, Level B (cirrhosis)
   b. LDV/SOF for 12 weeks
1. Rating: Class I, Level A
   c. OMB/PTV-R + DAS with RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)
      i. Rating: Class I, Level A
   d. SIM + SOF for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis without the Q80K polymorphism) with or without weight-based RBV
      i. Rating: Class I, Level A
2. Treatment-naive patients with HCV genotype 1b infection
   a. DCV/SOF for 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (cirrhosis)
      i. Rating: Class I, Level B (no cirrhosis); Class IIA, Level B (cirrhosis)
   b. LDV/SOF for 12 weeks is recommended for treatment-naive patients with HCV genotype 1b infection.
      i. Rating: Class I, Level A
   c. OMB/PTV-R + DAS for 12 weeks is recommended for treatment-naive patients with HCV genotype 1b infection.
      i. Rating: Class I, Level A
   d. SIM + SOF or 24 weeks with or without weight-based RBV (cirrhosis)
      i. Rating: Class I, Level A
3. Treatment-naive patients with HCV genotype 2 infection.
   a. DCV/SOF for 12 weeks
      i. Rating: Class IIA, Level B
   b. SOF and weight-based RBV for 12 weeks
      i. Rating: Class I, Level A
      ii. Extending treatment to 16 weeks is recommended in patients with cirrhosis.
         1. Rating: Class IIB, Level C
4. Recommended regimen for treatment-naive patients with HCV genotype 3 infection.
   a. DCV/SOF for 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (cirrhosis)
      i. Rating: Class I, Level A (no cirrhosis); Class IIA, Level C (cirrhosis)
   b. SOF and weight-based RBV plus weekly PEG-IFN for 12 weeks is recommended for IFN-eligible
      i. Rating: Class I, Level A
   c. Daily SOF and weight-based RBV for 24 weeks
      i. Rating: Class I, Level A
5. Recommendations for treatment-naive patients with HCV genotype 4 infection
   a. LDV/SOF for 12 weeks
      i. Rating: Class IIB, Level B
   b. OMB/PTV-R and weight-based RBV for 12 weeks
      i. Rating: Class I, Level B
   c. SOF and weight-based RBV for 24 weeks
      i. Rating: Class IIA, Level B
   d. SOF and weight-based RBV plus weekly PEG-IFN for 12 weeks is an acceptable regimen for treatment-naive patients with HCV genotype 4 infection.
      i. Rating: Class II, Level B
New Safety Alerts:
In October 2015, the FDA released a drug safety communication warning that hepatitis C treatments OMB/PTV-R + DAS (Viekira Pak ®) and OMB/PTV-R (Technivie ®) can cause serious liver injury mostly in patients with underlying advanced liver disease. As a result, the drug labels were updated to include this risk. A review of adverse events identified cases of hepatic decompensation and liver failure in patients with underlying liver cirrhosis, some of which resulted in liver transplantation or death. These were reported mostly in patients who had evidence of advanced cirrhosis before starting treatment.

New Formulations or Indications:
In November, the FDA approved an expanded indication for LDV/SOF for the treatment of patients with genotypes 1, 4, 5, and 6 of CHC Virus, as well as patients co-infected with HIV. It was also approved to be used in combination with RBV for 12 weeks to treat certain patients with hepatitis C and cirrhosis. Supporting RCTs are included in Table 1.

Randomized Controlled Trials:
A total of 20 citations were manually reviewed from the literature search. After further review, 12 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical) or because of unapproved medication. Trials covered in the new drug evaluation section were also excluded. The remaining 5 trials are briefly described in the table below. Full abstracts are included in Appendix 2.

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Population</th>
<th>Primary Outcome</th>
<th>Results</th>
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<tbody>
<tr>
<td>ION-4</td>
<td>LDV/SOF x 12 weeks</td>
<td>Adults with HCV/HIV coinfection, treatment-naive and experienced, 20% cirrhosis; genotypes 1 and 4</td>
<td>SVR12</td>
<td>SVR12: 322/325 (96%) Relapse: 10/335 (3%)</td>
</tr>
<tr>
<td></td>
<td>*No comparator group</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SIRIUS</td>
<td>LDV/SOF +/- RBV x 12 weeks vs. LDV/SOF x 24 weeks</td>
<td>Treatment experienced with PEG/RBV and a protease inhibitor, HCV genotype 1 and compensated cirrhosis</td>
<td>SVR12</td>
<td>SVR12: LDV/SOF + RBV: 74/77 (96%) LDV/SOF: 75/77 (97%)</td>
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<tr>
<td>PHOTON-2</td>
<td>SOF + RBV foe 12-24 weeks (12 weeks for tx naive GT2)</td>
<td>Adults with treatment naive GT 1-4 and treatment experienced GT 2 and 3; HCV/HIV coinfection</td>
<td>SVR12</td>
<td>SVR12: GT1: 95/112 (85%) GT2: 17/19 (89%) (Treatment naive) GT2: 5/6 (83%) (Treatment experienced) GT3: 52/27 (91%) (Treatment naive) GT3: 42/49 (86%) (Treatment experienced) GT4: 26/31 (84%)</td>
</tr>
<tr>
<td>TURQUOISE1</td>
<td>OMB/PTV-R + DAS + RBV x</td>
<td>GT1; HCV/HIV coinfection; treatment naive</td>
<td>SVR12</td>
<td>SVR12:</td>
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</table>
Clinical Efficacy:
The FDA approval of DCV/SOF for patients with HCV GT3 was primarily based upon one pivotal Phase 3 single-arm (n=152), open-label trial (ALLY-3) conducted in the United States and Puerto Rico. The ALLY-3 trial (details in evidence table) evaluated HCV GT3 patients with compensated liver disease with and without cirrhosis for treatment duration of 12 weeks. The primary efficacy endpoint was SVR at 12 weeks post-treatment. Overall, DCV/SOF achieved an SVR of 89% (135/152). However, SVR rates were reduced in HCV GT3 patients with cirrhosis (63%, 20/32) compared to those without cirrhosis (96%, 115/120). As a result, DCV/SOF for 12 weeks may not be the optimal regimen for those with cirrhosis. No differences in SVRs were noted based upon age, gender, IL28B status, or baseline HCV RNA level. SVR rates were lower in patients with the Y93H polymorphism at baseline [54% (7/13), 95% CI (25%, 81%)] compared to those without [92% (128/139), 95% CI (86%, 96%)]. However, there is not a commercially available assay to detect the presence of this polymorphism leaving the clinical implications of it unknown.

The ALLY-3 trial has significant methodological flaws including an open label design with no active comparator. It did not define a noninferiority margin for determination of efficacy. The FDA analysis calculated it based on historical data and concluded that DCV/SOF achieved non-inferiority compared to SOF/RBV for 24 weeks (2%; 95% CI -4% to 9%). Based upon these results, the FDA approved the use of DCV/SOF for 12 weeks in HCV GT3 patients with compensated liver disease with or without cirrhosis. However, the FDA stated a limitation of use of this regimen was that SVR rates were lower in HCV GT3 patients with cirrhosis and that the optimal duration for HCV GT3 patients with cirrhosis has not been established. The FDA has required a postmarket requirement to conduct a trial to determine if a longer duration of treatment or addition of ribavirin improves the efficacy in subjects with cirrhosis. In the ALLY-3 Plus study (unpublished), 21/24 (6/6 with advanced fibrosis and 15/18 with cirrhosis) patients receiving 12 weeks of DCV+SOF+RBV achieved an SVR4, whereas 25/26 (8/8 with advanced fibrosis and 17/18 with cirrhosis) patients receiving 16 weeks of DCV+SOF+RBV achieved an SVR4. These data demonstrate that patients with GT3 infection and cirrhosis may benefit from extended treatment duration. However, longer term and more data are needed to confirm this.

Off-label Populations
DCV/SOF is recommended by the AASLD guidelines as a treatment option for patients with genotypes 1, 2, and 4 based on additional trials.

NEW DRUG EVALUATION: Daclatasvir (Daklinza®)
See Appendix 3 for Highlights of Prescribing Information from the manufacturer, including Black Boxed Warning 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.
The ALLY-2 trial is a phase 3 open label trial that assessed DCV/SOF for 8-12 weeks for the treatment in patients with genotypes 1-4 CHC coinfecting with HIV and HCV (n=203). Eighty three percent of patients were infected if GT1 and 54% were treatment naïve. Treatment naïve patients were randomized to receive either 12 weeks or 8 weeks of DCV/SOF and previously treated subjects received the regimen for 12 weeks. Ninety two (46%) patients had a fibrosis score of at least F3. The SVR rate was 96% in treatment-naïve patients with HCV GT1 infection who received 12 weeks of therapy and was 75.6% among previously untreated patients who received 8 weeks of treatment. However, only 9 of these patients had cirrhosis. Ninety seven % of previously treated subject maintained an SVR at 12 weeks post treatment. The SVR24 rates were only 92% in the two 12 week groups and 72% in the 8-week groups. There were more virologic breakthroughs in the 8-week group compared to subjects receiving 12 weeks of treatment suggesting that 12 weeks of therapy should be considered for patients with HIV-HCV infection.

A similar open-label phase 2 trial evaluated DCV/SOF in HCV subjects with GT 1, 2, or 3. This trial included a lead-in period with SOF to determine whether it would decrease the emergence of DCV resistant variants. A total of 44 subjects were infected with HCV GT 2 or 3, and 167 with GT 1 infection. In patients with GT 2 or 3, SVR was 91% (40/44) and in GT 1, SVR was 98% in previously untreated subjects and 95% in previously treated.

Overall, patients with cirrhosis were not adequately represented in these studies and the optimal duration of treatment for patients with cirrhosis remains unclear.

**Clinical Safety:**
Overall, the limited short-term data for DCV does not show cause for any serious safety concerns and because DCV was the third NS5A inhibitor the FDA Advisory committee was not required to meet prior to approval of DCV. Overall, approximately 1900 patients with HCV infection have been treated with daclatasvir in combination with other HCV agents in clinical trials. The safety assessment described in the prescribing information was primarily based on the Phase 3 clinical trial (ALLY-3) in patients with HCV GT3 chronic hepatitis C with compensated liver disease with and without cirrhosis.

The most common adverse reactions in the ALLY-3 trial were headache and fatigue. All adverse reactions were mild to moderate in severity. One subject experienced a serious adverse event that was considered unrelated to DCV and no subjects discontinued therapy for adverse events. Adverse events that occurred in in at least 5% of patients are included below:

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Headache</td>
<td>21 (14%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (14%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (5%)</td>
</tr>
</tbody>
</table>

Further review has identified a potential drug drug interaction with use of amiodarone co-administered with SOF in combination with another DAA, including DCV resulting in potential severe bradycardia. The FDA label includes a warning to avoid the combination of amiodarone with DCV/SOF.
Transient, asymptomatic elevations in lipase occurred in 2% of subjects in ALLY-3.

Pharmacology and Pharmacokinetic Properties:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Inhibitor of HCV nonstructural protein 5A (NS5A).</td>
</tr>
<tr>
<td>Oral Bioavailability</td>
<td>67%</td>
</tr>
<tr>
<td>Distribution and Protein Binding</td>
<td>Vd: 47L; Protein binding ~99%</td>
</tr>
<tr>
<td>Elimination</td>
<td>Feces (88%, 53% unchanged); urine (6.6%, primarily unchanged)</td>
</tr>
<tr>
<td>Half-Life</td>
<td>12 to 15 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Daclatasvir is a substrate of CYP3A, with CYP3A4 being the primary CYP isoform responsible for metabolism. Following single-dose oral administration of 25 mg 14C-daclatasvir in healthy subjects, the majority of radioactivity in plasma was predominately attributed to parent drug (97% or greater).</td>
</tr>
</tbody>
</table>

Comparative Clinical Efficacy:

Comparative Evidence Table

<table>
<thead>
<tr>
<th>Ref./Study Design</th>
<th>Drug Regimens/Duration</th>
<th>Patient Population</th>
<th>N</th>
<th>Efficacy Endpoints</th>
<th>ARR/NNT</th>
<th>Safety Outcomes</th>
<th>ARR/NNH</th>
<th>Risk of Bias/Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ALLY-3† Open, label phase 3 study</td>
<td>1. DCV 60 mg + SOF 400 mg once daily x 12 weeks</td>
<td>Demographics: 59%, male Median age 55 90% white 21% cirrhosis 66% treatment naive 61% with non –CC IL28B GT</td>
<td>ITT 152</td>
<td>SVR12 (Total): 1. 135/152 (89%) 95% CI (83%, 93%) Without Cirrhosis: 115/120 (96%); 95% CI 91-99% With Cirrhosis: 20/32 (63%); 95% CI 44-79%</td>
<td>NA</td>
<td>Discontinuations due to Adverse Events: 0</td>
<td>NA</td>
<td>Risk of Bias (low/high/unclear): Selection Bias: high; open-label; nonrandomized; no comparator group Performance Bias: high; open-label; no comparator group Detection Bias: high; open label Attrition Bias: low; overall low attrition Reporting Bias: unclear</td>
</tr>
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</table>

Primary Study Endpoint:

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

Clinically Relevant Endpoints:

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

Author: Herink Date: January 2016
### Key Inclusion Criteria:
- Adults ≥ 18 y/o, treatment naïve or treatment experienced, chronic genotype 3 infection, HCV-RNA levels ≥ 10,000 IU/ml

### Key Exclusion Criteria:
- Treatment experienced with a NS5A inhibitor, previous intolerance to SOF, coinfection with HIV or HBV, HCC, decompensation

### SVR12 (Treatment naïve):
- 1. 91/101 (90%); 95% CI 83-95%
- Without Cirrhosis: 80/82 (98%; 95% CI 91-100%)
- With Cirrhosis: 11/19 (58%); 95% CI 34-80%

### SVR12 (Treatment experienced):
- 44/51 (86%)
- 95% CI (74%, 94%)
- Without Cirrhosis: 35/38 (92%); 95% CI 74-94%
- With Cirrhosis: 9/13 (69%); 95% CI 39-91%

### N/A
- Discontinuations due to Adverse Events: 0

### Risk of Bias (low/high/unclear):
- Selection Bias: high; only treatment-naïve patients randomized.
- Performance Bias: high; open-label;
- Detection Bias: high; open label
- Attrition Bias: low; overall low attrition; ITT used
- Reporting Bias: unclear

### Applicability:
- Patient: Majority of patients GT1; less than 10% with cirrhosis in previously untreated patients
- Intervention: Appropriate intervention
- Comparator: No active comparator group to assess efficacy and safety of medication

### Outcomes:
- Surrogate outcome of SVR 12 used to evaluate efficacy.
- Setting: Monitoring and follow-up difficult to mirror in clinical practice in the hepatitis C patient population.

### Abbreviations [alphabetical order]:
- AR = absolute risk reduction; CI = confidence interval; DCV = daclatasvir; GT = genotype; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OMB =
NEW DRUG EVALUATION: ombitasvir/paritaprevir/ritonavir (OMB/PTV-R) (Technivie®)

See Appendix 4 for Highlights of Prescribing Information from the manufacturer, including Black Boxed Warning 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:

OMB/PTV-R was approved for genotype 4 (GT4) CHC without cirrhosis based on the pivotal PEARL-1 trial which was a randomized, open-label phase 2b study randomized to receive therapy with or without RBV for 12 weeks in treatment-naïve and treatment-experienced patients. Treatment naïve patients were randomly assigned to receive treatment with or without RBV, while treatment experienced patients only received the treatment regimen containing ribavirin, as they were randomized later after the realization that the RBV regimen. Treatment experienced patients were limited to those who have failed treatment with pegylated interferon and ribavirin. All genotype 1b-infected patients without cirrhosis were enrolled and completed treatment before enrolment of the genotype 4-infected treatment-naïve patients to allow for a sequential evaluation of the two-direct-acting antiviral drug regimen in these two patient populations. Patients with cirrhosis were excluded from the study. There was no significant difference in SVR rates in treatment-naïve patients between those who received RBV and those who did not (100% vs. 91%; Mean difference –9.16%; 95% CI –19.61 to 1.29; P=0.086). In the treatment-experienced group and receiving ribavirin, 100% of patients achieved an SVR. Three treatment naïve patients without RBV had a virological failure and no patients who received RBV had a virological failure. Overall, the patient population had more mild disease with 77% fibrosis F0-F2 and no cirrhotics included in the study and the majority of the subjects were from Europe, limiting the generalizability of the results to clinical practice.

Clinical Safety:
Overall, treatment was well tolerated but based on limited short term data. The most commonly reported adverse reactions with an incidence greater than 10% in clinical trials were headache, asthenia, fatigue, nausea and insomnia. No patients reported any serious adverse events related to study drug or adverse events resulting in discontinuation of therapy. The following table displays adverse reactions that occurred in greater than 5% of subjects.
Elevations of liver enzymes to greater than 5 times the upper limit of normal occurred in approximately 1% of subjects which were typically asymptomatic. An unanswered safety question is the long-term effects of OMB/PTV-R on liver function.

Pharmacology and Pharmacokinetic Properties:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ombitasvir, paritaprevir, ritonavir + RBV 12 Weeks N = 91</th>
<th>Ombitasvir, paritaprevir, ritonavir 12 Weeks N = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Insomnia</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Pruritus*</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Skin reactions$^*$</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

Combines 2 direct-acting hepatitis C virus antiviral agents with distinct mechanisms of action. Ombitasvir inhibits HCV NS5A, and interferes with viral RNA replication and virion assembly. Paritaprevir inhibits HCV NS3/4A protease and interferes with HCV coded polyprotein cleavage necessary for viral replication. Ritonavir is not active against HCV. Ritonavir is a potent CYP3A inhibitor that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure (ie, AUC).

Oral Bioavailability
- Ombitasvir: ~48%; Paritaprevir: ~53%; Ritonavir: Not evaluated

Distribution and Protein Binding
- Ombitasvir: Vd: 173 L; Paritaprevir: Vd: 103 L; Ritonavir: Vd: Not evaluated

Elimination
- Ombitasvir: Feces (~90%, mainly as unchanged drug); urine (<2%, mainly as unchanged drug)
- Paritaprevir: Feces (~88%, mainly as metabolites); urine (~9%, mainly as metabolites)
- Ritonavir: Feces (~86%); urine (~11%)

Half-Life
- Ombitasvir: 21 to 25 hours; Paritaprevir: 5.5 hours; Ritonavir: 4 hours

Metabolism
- Ombitasvir: Metabolized by amide hydrolysis and oxidative metabolism
- Paritaprevir: Metabolized by CYP3A4 and to a lesser extent CYP3A5
Comparative Clinical Efficacy:
Clinically Relevant Endpoints:
1) Hepatocellular Carcinoma
2) Mortality
3) Liver Transplant
4) Discontinuation Rates Due to Adverse Events

Primary Study Endpoint:
2) Sustained Virologic Response at week 12 after the end of treatment (SVR12)

Comparative Evidence Table

<table>
<thead>
<tr>
<th>Ref./ Study Design</th>
<th>Drug Regimens/ Duration</th>
<th>Patient Population</th>
<th>N</th>
<th>Efficacy Endpoints</th>
<th>ARR/NNT</th>
<th>Safety Outcomes</th>
<th>ARR/NNH</th>
<th>Risk of Bias/ Applicability</th>
</tr>
</thead>
</table>
| 1. PEARL-1st phase 2b, randomized, open-label trial | Treatment-naive
1. OMB/PTV-R x 12 weeks 2. OMB/PTV-R + RBV x 12 weeks | Demographics: 86% from Europe Age 48 y/o Key Inclusion Criteria: Adults ≥ 18 y/o, treatment naive or treatment experienced, chronic genotype 4 infection, HCV-RNA levels ≥ 10,000 IU/ml Key Exclusion Criteria: Cirrhosis, HBV, HIV, other causes of liver disease | mITT TN 1. 44 2. 42 TE 1. 49 | SVR12: Treatment-naive 1. 91% (95% CI 78.3-97.5%) 2. 100% (95% CI 91.6-100%) Mean difference −9.16%; 95% CI −19.61 to 1.29 P=0.086 Treatment-experienced 1. 100% (92.7-100%) | NA | Discontinuations due to Adverse Events: 0 | NA | Risk of Bias (low/high/unclear): Selection Bias: high; only treatment naive subjects were randomized to receive therapy with ribavirin or no ribavirin using a computer generated randomization list. Treatment experienced subjects were not randomized. More patients in the group w/o RBV had F0-F1 fibrosis score (86% vs. 79%) Performance Bias: high; open-label Detection Bias: high; open label Attrition Bias: low; overall low attrition and ITT performed Reporting Bias: unclear |

Applicability:
Patient: Almost all white patients; included patients with more mild disease severity (77% F0-F2) with a low percentage of cirrhotics and overall higher baseline HCV RNA level; majority of patients from Europe (86%). Treatment experienced patients were limited to those who have failed treatment with PEG/RBV.
Intervention: Appropriate intervention Comparator: No active comparator group besides addition of RBV to truly assess efficacy of OMB/PTV-R Outcomes: Surrogate outcome of SVR 12 used
to evaluate efficacy.
Setting: Multicenter sites in Europe and US

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OMB = ombitasvir; PP = per protocol; PTV = paritaprevir; R = ritonavir; RBV = ribavirin; SVR12 = sustained virologic response at 12 weeks after treatment; TN = Treatment naïve; TE = treatment experienced

References:


Author: Herink

Date: January 2016


22. Daclatasvir. Drugs@FDA. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206843Orig1s000TOC.cfm.

Author: Herink

Date: January 2016
### Appendix 1: Current Status on Preferred Drug List

<table>
<thead>
<tr>
<th>ROUTE</th>
<th>FORMULATION</th>
<th>BRAND</th>
<th>GENERIC</th>
<th>PDL</th>
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</thead>
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<tr>
<td>ORAL</td>
<td>TABLET</td>
<td>HARVONI</td>
<td>LEDIPASVIR/SOFOSBUVIR</td>
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<tr>
<td>ORAL</td>
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<td>VIEKIRA PAK</td>
<td>OMBITA/PARITAP/ RITON/DASABUVIR</td>
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<tr>
<td>SUB-Q</td>
<td>KIT</td>
<td>PEGINTRON</td>
<td>PEGINTERFERON ALFA-2B</td>
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</tr>
<tr>
<td>SUB-Q</td>
<td>PEN IJ KIT</td>
<td>PEGINTRON REDIPEN</td>
<td>PEGINTERFERON ALFA-2B</td>
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<td>PEGASYS PROCLICK</td>
<td>PEGINTERFERON ALFA-2A</td>
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<td>PEGASYS</td>
<td>PEGINTERFERON ALFA-2A</td>
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<td>RIBAVIRIN</td>
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<td>RIBAVIRIN</td>
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<td>SIMEPREVIR SODIUM</td>
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<td>RIBAVIRIN</td>
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<tr>
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<td>TAB DS PK</td>
<td>RIBASPHERE RIBAPAK</td>
<td>RIBAVIRIN</td>
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</tbody>
</table>
Appendix 2: Abstracts of Clinical Trials


   BACKGROUND: Effective treatment for hepatitis C virus (HCV) in patients coinfected with human immunodeficiency virus type 1 (HIV-1) remains an unmet medical need.

   METHODS: We conducted a multicenter, single-group, open-label study involving patients coinfected with HIV-1 and genotype 1 or 4 HCV receiving an antiretroviral regimen of tenofovir and emtricitabine with efavirenz, rilpivirine, or raltegravir. All patients received ledipasvir, an NS5A inhibitor, and sofosbuvir, a nucleotide polymerase inhibitor, as a single fixed-dose combination for 12 weeks. The primary end point was a sustained virologic response at 12 weeks after the end of therapy.

   RESULTS: Of the 335 patients enrolled, 34% were black, 55% had been previously treated for HCV, and 20% had cirrhosis. Overall, 322 patients (96%) had a sustained virologic response at 12 weeks after the end of therapy (95% confidence interval [CI], 93 to 98), including rates of 96% (95% CI, 93 to 98) in patients with HCV genotype 1a, 96% (95% CI, 89 to 99) in those with HCV genotype 1b, and 100% (95% CI, 63 to 100) in those with HCV genotype 4. Rates of sustained virologic response were similar regardless of previous treatment or the presence of cirrhosis. Of the 13 patients who did not have a sustained virologic response, 10 had a relapse after the end of treatment. No patient had confirmed HIV-1 virologic rebound. The most common adverse events were headache (25%), fatigue (21%), and diarrhea (11%). No patient discontinued treatment because of adverse events.

   CONCLUSIONS: Ledipasvir and sofosbuvir for 12 weeks provided high rates of sustained virologic response in patients coinfected with HIV-1 and HCV genotype 1 or 4. (Funded by Gilead Sciences; ION-4 ClinicalTrials.gov number, NCT02073656.).

BACKGROUND: Patients with cirrhosis resulting from chronic hepatitis C virus (HCV) infection are at risk of life-threatening complications, but consistently achieve lower sustained virological response (SVR) than patients without cirrhosis, especially if treatment has previously failed. We assessed the efficacy and safety of the NS5A inhibitor ledipasvir and the nucleotide polymerase inhibitor sofosbuvir, with and without ribavirin.

METHODS: In this multicentre, double-blind trial, between Oct 21, 2013, and Oct 30, 2014, we enrolled patients with HCV genotype 1 and compensated cirrhosis who had not achieved SVR after successive treatments with pegylated interferon and protease-inhibitor regimens at 20 sites in France. With a computer-generated randomisation sequence, patients were assigned in a 1:1 ratio to receive placebo matched in appearance to study drugs for 12 weeks followed by once daily combination fixed-dose tablets of 90 mg ledipasvir and 400 mg sofosbuvir plus weight-based ribavirin for 12 weeks, or ledipasvir-sofosbuvir plus placebo once daily for 24 weeks. The primary endpoint was SVR 12 weeks after the end of treatment (SVR12), for which 95% CIs were calculated with the Clopper-Pearson method. This study is registered with ClinicalTrials.gov, number NCT01965535.

FINDINGS: Of 172 patients screened, 155 entered randomisation, 77 were assigned to receive ledipasvir-sofosbuvir plus ribavirin and 78 ledipasvir-sofosbuvir. 114 (74%) were men, 151 (97%), were white, 98 (63%) had HCV genotype 1a, and 145 (94%) had non-CC IL28B alleles. SVR12 rates were 96% (95% CI 89-99) for patients in the ledipasvir-sofosbuvir plus ribavirin group and 97% (91-100) in the ledipasvir-sofosbuvir group. One patient discontinued treatment because of adverse events while receiving only placebo. The most frequent adverse events were asthenia and headache, pruritus, and fatigue.

INTERPRETATION: Ledipasvir-sofosbuvir plus ribavirin for 12 weeks and ledipasvir-sofosbuvir for 24 weeks provided similarly high SVR12 rates in previous non-responders with HCV genotype 1 and compensated cirrhosis. The shorter regimen, when given with ribavirin, might, therefore, be useful to treat treatment-experienced patients with cirrhosis if longer-term treatment is not possible.

BACKGROUND: Although interferon-free regimens are approved for patients co-infected with HIV and genotype-2 or genotype-3 hepatitis C virus (HCV), interferon-based regimens are still an option for those co-infected with HIV and HCV genotypes 1 or 4. These regimens are limited by clinically significant toxic effects and drug interactions with antiretroviral therapy. We aimed to assess the efficacy and safety of an interferon-free, all-oral regimen of sofosbuvir plus ribavirin in patients with HIV and HCV co-infection.

METHODS: We did this open-label, non-randomised, uncontrolled, phase 3 study at 45 sites in seven European countries and Australia. We enrolled patients (aged ≥18 years) co-infected with stable HIV and chronic HCV genotypes 1-4, including those with compensated cirrhosis. Once-daily sofosbuvir (400 mg) plus twice-daily ribavirin (1000 mg in patients with bodyweights <75 kg and 1200 mg in those with weights ≥75 kg) was given for 24 weeks to all patients except treatment-naive patients with genotype-2 HCV, who received a 12-week regimen. The primary efficacy endpoint was sustained virological response 12 weeks after treatment. We did analysis by modified intention to treat. This study is registered with ClinicalTrials.gov, number NCT01783678.

FINDINGS: Between Feb 7, 2013, and July 29, 2013, we enrolled 275 eligible patients, of whom 262 (95%) completed treatment; 274 patients were included in the final analysis. Overall rates of sustained virological response 12 weeks after treatment were 85% (95% CI 77-91) in patients with genotype-1 HCV, 88% (69-98) in patients with genotype-2 HCV, 89% (81-94) in patients with genotype-3 HCV, and 84% (66-95) in patients with genotype-4 HCV. Response rates in treatment-naive patients with HCV genotypes 2 or 3 (89% [95% CI 67-99] and 91% [81-97], respectively) were similar to those in treatment-experienced patients infected with those genotypes (83% [36-100] and 86% [73-94], respectively). There was no emergence of sofosbuvir-resistance mutations in patients with HCV viral relapse. Six (2%) patients discontinued treatment because of adverse events. The most common adverse events were fatigue, insomnia, asthenia, and headache. Four (1%) patients had serious adverse events regarded as related to study treatment. Additionally, four (1%) patients receiving antiretroviral treatment had a transient HIV viral breakthrough; however, none required changes in antiretroviral regimen.

INTERPRETATION: Sofosbuvir and ribavirin provided high rates of sustained virological response after 12 weeks of treatment in treatment-naive and treatment-experienced patients co-infected with HIV and HCV genotypes 1-4. The characteristics of this interferon-free combination regimen make sofosbuvir plus ribavirin a useful treatment option for this patient population.

IMPORTANCE: Patients co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are at high risk for liver disease progression. However, interferon-based treatments for HCV infection have significant toxicities, limiting treatment uptake.

OBJECTIVE: To assess the all-oral 3 direct-acting antiviral (3D) regimen of ombitasvir, paritaprevir (co-dosed with ritonavir [paritaprevir/r]), dasabuvir, and ribavirin in HCV genotype 1-infected adults with HIV-1 co-infection, including patients with cirrhosis.

DESIGN, SETTING, AND PARTICIPANTS: TURQUOISE-I is a randomized, open-label study. Part 1a of this pilot study was conducted at 17 sites in the United States and Puerto Rico between September 2013 and August 2014 and included 63 patients with HCV genotype 1 and HIV-1 co-infection who were HCV treatment-naive or had history of prior treatment failure with peginterferon plus ribavirin therapy. The study allowed enrollment of patients, including those with cirrhosis, with a CD4+ count of 200/mm3 or greater or CD4+ percentage of 14% or more and plasma HIV-1 RNA suppressed while taking a stable atazanavir- or raltegravir-inclusive antiretroviral regimen.

INTERVENTIONS: Ombitasvir/paritaprevir/r, dasabuvir, and ribavirin for 12 or 24 weeks of treatment as randomized.

MAIN OUTCOMES AND MEASURES: The primary assessment was the proportion of patients with sustained virologic response (HCV RNA <25 IU/mL) at posttreatment week 12 (SVR12).

RESULTS: Among patients receiving 12 or 24 weeks of 3D and ribavirin, SVR12 was achieved by 29 of 31 (94%; 95% CI, 79%-98%) and 29 of 32 patients (91%; 95% CI, 76%-97%), respectively. Of the 5 patients who did not achieve SVR, 1 withdrew consent, 2 had confirmed virologic relapse or breakthrough, and 2 patients had clinical history and phylogenetic evidence consistent with HCV reinfection. The most common treatment-emergent adverse events were fatigue (48%), insomnia (19%), nausea (18%), and headache (16%). Adverse events were generally mild, with none reported as serious or leading to discontinuation. No patient had a confirmed HIV-1 breakthrough of 200 copies/mL or greater during treatment.

CONCLUSIONS AND RELEVANCE: In this open-label, randomized uncontrolled study, treatment with the all-oral, interferon-free 3D-plus-ribavirin regimen resulted in high SVR rates among patients co-infected with HCV genotype 1 and HIV-1 whether treated for 12 or 24 weeks. Further phase 3 studies of this regimen are warranted in patients with co-infection.

BACKGROUND & AIMS: There are no effective and safe treatments for chronic hepatitis C virus (HCV) infection of patients who have advanced liver disease.

METHODS: In this phase 2, open-label study, we assessed treatment with the NS5A inhibitor ledipasvir, the nucleotide polymerase inhibitor sofosbuvir, and ribavirin in patients infected with HCV genotypes 1 or 4. Cohort A enrolled patients with cirrhosis and moderate or severe hepatic impairment who had not undergone liver transplantation. Cohort B enrolled patients who had undergone liver transplantation: those without cirrhosis; those with cirrhosis and mild, moderate, or severe hepatic impairment; and those with fibrosing cholestatic hepatitis. Patients were assigned randomly (1:1) to receive 12 or 24 weeks of a fixed-dose combination tablet containing ledipasvir and sofosbuvir, once daily, plus ribavirin. The primary end point was sustained virologic response at 12 weeks after the end of treatment (SVR12).

RESULTS: We enrolled 337 patients, 332 (99%) with HCV genotype 1 infection and 5 (1%) with HCV genotype 4 infection. In cohort A (nontransplant), SVR12 was achieved by 86%-89% of patients. In cohort B (transplant recipients), SVR12 was achieved by 96%-98% of patients without cirrhosis or with compensated cirrhosis, by 85%-88% of patients with moderate hepatic impairment, by 60%-75% of patients with severe hepatic impairment, and by all 6 patients with fibrosing cholestatic hepatitis. Response rates in the 12- and 24-week groups were similar. Thirteen patients (4%) discontinued the ledipasvir and sofosbuvir combination prematurely because of adverse events; 10 patients died, mainly from complications related to hepatic decompensation.

CONCLUSION: The combination of ledipasvir, sofosbuvir, and ribavirin for 12 weeks produced high rates of SVR12 in patients with advanced liver disease, including those with decompensated cirrhosis before and after liver transplantation. ClinTrials.gov: NCT01938430.
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DAKLINZA safely and effectively. See full prescribing information for DAKLINZA.

DAKLINZA™ (daclatasvir) tablets, for oral use
Initial U.S. Approval: 2015

---------------------------------------------------------INDICATIONS AND USAGE---------------------------------------------------------
DAKLINZA is a hepatitis C virus (HCV) NS5A inhibitor indicated for use with sofosbuvir for the treatment of chronic HCV genotype 3 infection. (1)

Limitations of Use:
• Sustained virologic response (SVR) rates are reduced in patients with cirrhosis. (14)

---------------------------------------------------------DOSAGE AND ADMINISTRATION---------------------------------------------------------
• 60 mg taken orally once daily with or without food in combination with sofosbuvir. (2.1)
• Recommended treatment duration: 12 weeks. (2.1)
• Dose modification: Reduce dosage to 30 mg once daily with strong CYP3A inhibitors and increase dosage to 90 mg once daily with moderate CYP3A inducers. (2.2)

---------------------------------------------------------DOSAGE FORMS AND STRENGTHS---------------------------------------------------------
• Tablet: 60 mg and 30 mg (3)

---------------------------------------------------------CONTRAINDICATIONS---------------------------------------------------------
• Strong inducers of CYP3A, including phenytoin, carbamazepine, rifampin, and St. John’s wort. (4)

---------------------------------------------------------WARNINGS AND PRECAUTIONS---------------------------------------------------------
• Bradycardia When Coadministered with Sofosbuvir and Amiodarone: Serious symptomatic bradycardia may occur in patients taking amiodarone with sofosbuvir in combination with another HCV direct-acting agent, including DAKLINZA, particularly in patients also receiving beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with DAKLINZA in combination with sofosbuvir is not recommended. In patients with no alternative treatment options, cardiac monitoring is recommended. (5.2, 6.2, 7.3)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------------------------------------------------------DRUG INTERACTIONS---------------------------------------------------------
• Drug Interactions: Coadministration of DAKLINZA can alter the concentration of other drugs and other drugs may alter the concentration of daclatasvir. Consult the full prescribing information before use for contraindicated drugs and other potential drug-drug interactions. (2.2, 4, 5.1, 7, 12.3)

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

Revised: 7/2015
Appendix 4: Highlights of Prescribing Information (Ombitasvir, paritaprevir and ritonavir)

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

TECHNIVIE (ombitasvir, paritaprevir and ritonavir) tablets, for oral use Initial U.S. Approval: 2015

----------------------------- RECENT MAJOR CHANGES -----------------------------
Indications and Usage, Removed-Limitations of Use (1) 10/2015
Dosage and Administration, Testing Prior to Initiation of TECHNIVIE (2.1) 10/2015
Dosage and Administration, Recommended Dosage in Adults (2.2) 10/2015
Dosage and Administration, Dosage in Patients with Hepatic Impairment (2.3) 10/2015
Contraindications (4) 10/2015
Warnings and Precautions (5.1) 10/2015

----------------------------- INDICATIONS AND USAGE -----------------------------
TECHNIVIE is a fixed-dose combination of ombitasvir, a hepatitis C virus NS5A inhibitor, paritaprevir, a hepatitis C virus NS3/4A protease inhibitor, and ritonavir, a CYP3A inhibitor and is indicated in combination with ribavirin for the treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection without cirrhosis. (1)

----------------------------- DOSAGE AND ADMINISTRATION -----------------------------
- Testing Prior to Initiation: Assess baseline hepatic laboratory and clinical parameters. (2.1)
- Recommended dosage: Two tablets taken orally once daily (in the morning) with a meal without regard to fat or calorie content. TECHNIVIE is recommended to be used in combination with ribavirin. (2.2)

<table>
<thead>
<tr>
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<th>Treatment</th>
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<tr>
<td>Genotype 4 without cirrhosis</td>
<td>TECHNIVIE + ribavirin*</td>
<td>12 weeks</td>
</tr>
<tr>
<td>*TECHNIVIE administered without ribavirin for 12 weeks may be considered for treatment-naïve patients who cannot take or tolerate ribavirin [see Microbiology (12.4) and Clinical Studies (14)].</td>
<td></td>
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----------------------------- DOSAGE FORMS AND STRENGTHS -----------------------------
Tablets: 12.5 mg ombitasvir, 75 mg paritaprevir, 50 mg ritonavir. (3)

----------------------------- CONTRAINDICATIONS -----------------------------
The contraindications to ribavirin also apply to this combination regimen. (4)

- Patients with moderate to severe hepatic impairment (4, 5.1, 8.6, 12.3)
- Co-administration with drugs that are highly dependent on CYP3A for clearance, moderate and strong inducers of CYP3A. (4)
- Known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome). (4)

----------------------------- WARNINGS AND PRECAUTIONS -----------------------------
- Hepatic Decompensation and Hepatic Failure in Patient with Cirrhosis: Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported mostly in patients with advanced cirrhosis. Discontinue treatment in patients who develop evidence of hepatic decompensation. (5.1)
- ALT Elevations: Discontinue ethinyl estradiol-containing medications prior to starting TECHNIVIE (alternative contraceptive methods are recommended). Perform hepatic laboratory testing on all patients during the first 4 weeks of treatment. For ALT elevations on TECHNIVIE, monitor closely and follow recommendations in full prescribing information. (5.2)
- Risks Associated With Ribavirin Combination Treatment: The warnings and precautions for ribavirin also apply to this combination regimen. (5.3)
- Drug Interactions: The concomitant use of TECHNIVIE and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of TECHNIVIE. (5.4)

----------------------------- ADVERSE REACTIONS -----------------------------
The most commonly reported adverse reactions (incidence greater than 10% of subjects, all grades) observed with treatment with ombitasvir, paritaprevir and ritonavir with ribavirin for 12 weeks were asthenia, fatigue, nausea and insomnia. (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 -----------------------------
Co-administration of TECHNIVIE can alter the plasma concentrations of some drugs and some drugs may alter the plasma concentrations of TECHNIVIE. The potential for drug-drug interactions must be considered before and during treatment. Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.4, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015
Appendix 5: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2015, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 10, 2014
1 Hepatitis C/ or hepatitis c virus.mp. or Hepatitis C, Chronic 43,112
2 Antiviral Agents/ or direct acting antivirals.mp 49116
3 sofosbuvir.mp 283
4 ledipasvir.mp 74
5 ombitasvir.mp. 33
6 daclatasvir.mp. 129
7 dasabuvir.mp. 27
8 1 or 2 44131
9 3 or 4 or 5 or 6 or 7 or 8 49149
10 9 and 10 12809
11 limit 11 to (english language and humans and yr="2015 -Current" and (clinical trial, phase ii or clinical trial, phase iii or controlled clinical trial or meta analysis or systematic reviews)) 20
12 from 12 keep 2, 11, 17-18, 20-24, 27-28, 31... 8
# Appendix 6: Current Prior Authorization 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

<table>
<thead>
<tr>
<th>Step</th>
<th>Question</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>What diagnosis is being treated?</td>
<td>Record ICD10 code.</td>
</tr>
<tr>
<td>2.</td>
<td>Is the request for treatment of Chronic Hepatitis C Virus?</td>
<td>Yes: Go to #3</td>
</tr>
<tr>
<td>3.</td>
<td>What regimen is requested?</td>
<td>Document and Go to #4.</td>
</tr>
<tr>
<td>4.</td>
<td>Does the regimen contain a drug not yet reviewed by P&amp;T?</td>
<td>Yes: Go to #5</td>
</tr>
<tr>
<td>Approval Criteria</td>
<td>Yes:</td>
<td>No:</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>------</td>
<td>-----</td>
</tr>
<tr>
<td>5. Will the prescriber change to a preferred product already reviewed for efficacy and safety by the P&amp;T Committee?</td>
<td>Inform Provider of covered alternatives in class</td>
<td>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.</td>
</tr>
<tr>
<td>6. Is the medication being prescribed by or in consultation with a hepatologist or gastroenterologist with experience in Hepatitis C?</td>
<td>Go to #7.</td>
<td>Pass to RPh; deny for appropriateness. Forward to DMAP for further review to determine appropriateness of prescriber.</td>
</tr>
<tr>
<td>7. 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?</td>
<td>Go to #8.</td>
<td>Go to #9.</td>
</tr>
<tr>
<td><strong>Note:</strong> Patients with a MELD score &gt;11 may be eligible for therapy, but only after review by the DMAP medical director. If patient has Metavir F0-F2, a treatment option remains pegylated interferon and ribavirin; refer to that specific PA Criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Does the patient have decompensated cirrhosis?</td>
<td>Pass to RPh; deny for appropriateness</td>
<td>Go to #11</td>
</tr>
<tr>
<td>Approval Criteria</td>
<td>Yes: Go to #11.</td>
<td>No: Go to 10.</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
</tbody>
</table>
| 9. 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?  
  a. Type 2 or 3 cryoglobulinemia with end-organ manifestations (vasculitis)  
  b. Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis                                                                 |                                                                                                                                                              |                                                 |
| 10. Does the patient have Hepatitis C Virus in the transplant setting, including the following scenarios:  
  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  
  And expected survival from non-HCV associated morbidity should be greater than 5 years?                                                                 | Yes: Go to #11.                                                                                      | No: Pass to RPh; deny for medical appropriateness.  
  Note: Other scenarios not included can be brought to the Medical Director on a case by case basis. |
<p>| 11. 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?                                                                 | Yes: Go to #12.                                                                                      | No: Pass to RPh; deny for appropriateness.         |
| 12. Does the patient have significant renal impairment (CrCl ≤30 mL/min) or end state renal disease (ESRD)?                                                                                                          | Yes: Pass to RPh; deny for appropriateness.                                                         | No: Go to #13.                                   |
| 13. Does the patient have a baseline HCV RNA level?                                                                                                                                                               | Yes: Record value and go to #14                                                                    | No: Pass to RPh. Request provider obtains baseline lab value. |</p>
<table>
<thead>
<tr>
<th>Approval Criteria</th>
<th>Yes: Approve for 8-12 weeks based on dosing and administration table.</th>
<th>No: Go to #16 If prescribed other DAA, encourage prescriber to use our preferred product</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. What Hepatitis C genotype is the patient? Record Genotype:</td>
<td>Record Genotype and go to #15.</td>
<td></td>
</tr>
<tr>
<td>15. 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?</td>
<td>Yes: Approve for 8-12 weeks based on dosing and administration table.</td>
<td>No: Go to #16 If prescribed other DAA, encourage prescriber to use our preferred product</td>
</tr>
<tr>
<td>16. Is the prescribed drug sofosbuvir (Solvaldi®)?</td>
<td>Yes: Go to #17</td>
<td>No: Go to #18</td>
</tr>
<tr>
<td>17. Does the patient have Genotype 2 hepatitis C infection?</td>
<td>Yes: Approve for 12 weeks based on dosing and administration table below</td>
<td>No: Go to #18 If prescribed other DAA, encourage prescriber to use our preferred product</td>
</tr>
<tr>
<td>18. Is the prescribed drug ombitasvir, paritaprevir, and ritonavir; dasabuvir (Viekira Pak®)?</td>
<td>Yes: Go to #19</td>
<td>No: Pass to RPh; deny for appropriateness. Encourage prescriber to use our preferred DAA.</td>
</tr>
<tr>
<td>19. Has the patient been off all ethinyl estradiol containing products for at least a week OR is willing to discontinue any products one week prior to starting therapy?</td>
<td>Yes: Go to #20</td>
<td>No: Pass to RPh; deny for appropriateness.</td>
</tr>
<tr>
<td>Approval Criteria</td>
<td>Yes:</td>
<td>No:</td>
</tr>
<tr>
<td>-------------------</td>
<td>------</td>
<td>-----</td>
</tr>
<tr>
<td>20. If the patient was or is on any other medications that due to drug-drug interactions are contraindicated with the use of Viekira Pak (See Table 2 below), has the patient stopped this medication at least a week ago or is willing to discontinue this medication (and it is appropriate) at least one week prior to starting therapy?</td>
<td>Go to #21</td>
<td>Pass to RPh; deny for appropriateness.</td>
</tr>
<tr>
<td>If the patient is not on any medications in Table 2 that are contraindicated, go to #21.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. Does the patient have HIV coinfection?</td>
<td>Go to #22</td>
<td>Go to #23</td>
</tr>
<tr>
<td>22. Is the patient not receiving suppressive antiretroviral therapy (who may be at increased risk of HIV-1 protease inhibitor drug resistance) OR on therapy with significant antiretroviral drug-interactions (efavirenz, darunavir/ritonavir, lopinavir/ritonavir, rilpivirine).</td>
<td>Pass to RPh; deny for appropriateness.</td>
<td>Go to #23</td>
</tr>
<tr>
<td>23. Is the patient treatment naïve with or without cirrhosis or treatment experienced without cirrhosis?</td>
<td>Approve for 12 weeks based on appropriate dosing and administration from table below</td>
<td>Go to #24</td>
</tr>
<tr>
<td>24. Has the patient failed previous therapy with a direct acting antiviral?</td>
<td>Pass to RPh; deny for appropriateness. Use of Viekira has not been studied in this population.</td>
<td>Go to #25</td>
</tr>
<tr>
<td>25. If the patient failed previous therapy with peginterferon/ribavirin dual therapy, did the patient relapse or have a partial response?</td>
<td>Approve for 12 weeks based on dosing and administration table below</td>
<td>Go to #26</td>
</tr>
<tr>
<td>26. Does the patient have cirrhosis and had a previous null response to dual therapy with peginterferon and ribavirin therapy or a post-liver transplant patient?</td>
<td>Approve for 24 weeks based on dosing and administration table below</td>
<td>Pass to RPh; deny for appropriateness. Encourage</td>
</tr>
</tbody>
</table>
### Table 1: Dosage and Administration:

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>Without Cirrhosis and HCV RNA &lt; 6 million IU/mL</th>
<th>LDV/SOF 1 tablet QDay</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve</td>
<td>Without Cirrhosis and HCV RNA ≥ 6 million IU/mL</td>
<td>LDV/SOF 1 tablet QDay</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>Without Cirrhosis; Genotype 1b</td>
<td>Paritaprevir/R+Ombitasvir+Dasabuvir</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>Without Cirrhosis; Genotype 1a</td>
<td>Paritaprevir/R+Ombitasvir+Dasabuvir + RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td>With Cirrhosis</td>
<td>LDV/SOF 1 tablet QDay</td>
<td>Paritaprevir/R+Ombitasvir+Dasabuvir + RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Experienced</td>
<td>Without Cirrhosis</td>
<td>LDV/SOF 1 tablet QDay + RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>With Cirrhosis</td>
<td>Paritaprevir/R+Ombitasvir+Dasabuvir + RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 weeks-24 weeks*</td>
<td></td>
</tr>
</tbody>
</table>

**Genotype 2**

| Naïve                         | With or Without Cirrhosis                        | SOF 400 mg QDay + RBV | 12 weeks** |

**Genotype 3**

| Naïve or Experienced          | With or Without Cirrhosis                        | DCV/SOF 1 tablet QDAY  | 12-24 weeks*** |
| Naïve or Experienced          | With or Without Cirrhosis                        | LDV/SOF 1 tablet QDay + RBV | 12 weeks |

**Genotype 4**

| Naïve or Experienced          | Without Cirrhosis                                 | Paritaprevir/R + Ombitasvir + RBV | 12 weeks |

**Genotype 4 and 6**

| Naïve or Experienced          | With or Without Cirrhosis                        | LDV/SOF 1 tablet QDay | 12 weeks |

*24 weeks of therapy with Paritaprevir/R+Ombitasvir+Dasabuvir + RBV should be reserved for treatment experienced, genotype 1a, null responders or post-liver transplant patients

**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®)

### Table 2: Drugs Contraindicated with Viekira Pak

<table>
<thead>
<tr>
<th>Alfuzosin HCL</th>
<th>Methylergonovine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>St. John’s Wort</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Lovastatin</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Pimozide</td>
</tr>
</tbody>
</table>

Author: Herink

Date: January 2016
<table>
<thead>
<tr>
<th>Gemfibrozil</th>
<th>Efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>Sildenafil*</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>Triazolam</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>Midazolam</td>
</tr>
<tr>
<td>Ergonovine</td>
<td></td>
</tr>
</tbody>
</table>

*When dosed as REVATIO for the treatment of pulmonary arterial hypertension (PAH)

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

**Implementation:** TBD; 10/15; 4/15; 1/15; 9/14; 7/14; 3/14