## Treatment-Naive Genotype 4 With Compensated Cirrhosis

### Recommended Regimens

#### Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 4 infection in patients with or without cirrhosis. ASTRAL-1 included 64 genotype 4-infected, treatment-naive patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (100%) \(^{[8]}\). The POLARIS-2 phase 3 study randomized DAA-naive patients (19% with compensated cirrhosis, overall) to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) or 12 weeks of sofosbuvir/velpatasvir. Of 57 patients with genotype 4 in the sofosbuvir/velpatasvir arm, 98% achieved SVR and 1 patient experienced relapse \(^{[1]}\). EXPEDITION-1 included 16 treatment-naive and -experienced genotype 4-infected participants with compensated cirrhosis. All 16 patients achieved SVR12. Baseline NS5A RASs were detected by next-generation sequencing (using a 15% detection cutoff) in 40% of 133 tested.

#### Glecaprevir/Pibrentasvir

EXPEDITION-1 was a multicenter, open-label, single-arm, phase 3 trial that enrolled 146 treatment-naive or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. Patients received the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks. Across all genotypes, 145/146 (99%) achieved SVR12 \(^{[2]}\). EXPEDITION-1 included 16 treatment-naive and -experienced genotype 4-infected participants with compensated cirrhosis. All 16 patients achieved SVR12. Baseline NS5A RASs were detected by next-generation sequencing (using a 15% detection cutoff) in 40% of 133 tested.

### Table: Recommended and Alternative Regimens

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
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<tbody>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)(^{b})</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)</td>
<td>12 weeks</td>
<td>IIa, B</td>
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<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>IIa, B</td>
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</tbody>
</table>

**ALTERNATIVE**

<table>
<thead>
<tr>
<th>DURATION</th>
<th>RATING</th>
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<tbody>
<tr>
<td>Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin(^{c})</td>
<td>12 weeks</td>
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</tbody>
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\(^{a}\) For **decompensated cirrhosis**, please refer to the appropriate section.

\(^{b}\) This is a 3-tablet coformulation. Please refer to the prescribing information.

\(^{c}\) Please see statement on FDA **warning** regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.
participants. Baseline NS5A RASs had no effect on SVR rates among treatment-naive and -experienced participants with genotype 4. Based on this study, a 12-week course of glecaprevir/pibrentasvir is recommended for genotype 4-infected, treatment-naive patients with compensated cirrhosis.

Elbasvir/Grazoprevir

A phase 2/3 trial evaluated 66 treatment-naive, genotype 4 patients treated with daily elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks. Ten patients had weight-based ribavirin added to the regimen and 56 did not. Six participants (9.1%) were cirrhotic and 28 (42.4%) had HIV/HCV coinfection. Overall, 97% (64/66) achieved SVR12. There was 1 treatment failure and 1 patient was lost to follow-up. The impact of ribavirin could not be assessed, however the addition of ribavirin numerically increased the SVR12 rate in treatment-experienced participants. Baseline RASs and subtype did not appear to impact SVR12 rates (Asselah, 2018c).

Ledipasvir/Sofosbuvir

The SYNERGY trial was an open-label study evaluating 12 weeks of ledipasvir (90 mg)/sofosbuvir (400 mg) in 21 genotype 4-infected patients, of whom 60% were treatment naive and 43% had advanced fibrosis (Metavir stage F3 or F4) (Kohli, 2015). One patient took the first dose and then withdrew consent. The 20 patients who completed treatment all achieved SVR12; thus, the SVR12 rate was 95% in the intention-to-treat analysis and 100% in the per-protocol analysis. Abergel and colleagues reported data from an open-label, single-arm study including 22 genotype 4-infected, treatment-naive patients (1 with cirrhosis) with an SVR12 rate of 95% (21/22) (Abergel, 2016). These pilot studies support the use of ledipasvir/sofosbuvir in patients with genotype 4 infection.

Alternative Regimen

Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

PEARL-I was a randomized, open-label phase 2b study that included a cohort of 86 treatment-naive patients with genotype 4 infection without cirrhosis who received 12 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg), with or without weight-based ribavirin. SVR12 rates were 100% (42/42) in the ribavirin arm and 90.9% (40/44) in the group not receiving ribavirin. Adverse effects were generally mild, with headache, asthenia, fatigue, and nausea most commonly reported. There were no discontinuations owing to adverse events (Hézode, 2015).

The AGATE-I trial randomized 120 treatment-naive and -experienced patients with genotype 4 infection and compensated cirrhosis to receive 12 weeks or 16 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated (Asselah, 2015a). Similarly, the AGATE-II trial offered 100 treatment-naive and -experienced (interferon-based regimens) noncirrhotic patients with genotype 4 infection paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin for 12 weeks. The SVR12 was 94%. Additionally, AGATE-II randomized 60 treatment-naive and -experienced genotype 4-infected patients with compensated cirrhosis to receive either 12 or 24 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR rate from the 12-week arm was 97%. These data support the use of a 12-week course of paritaprevir/ritonavir/ombitasvir plus ribavirin in treatment-experienced genotype 4 patients, including those with cirrhosis (Esmat, 2015).

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Related References


