**Recommended Regimens**

### Glecaprevir/Pibrentasvir

The SURVEYOR-II, part 3 trial evaluated the safety and efficacy of a 12-week or 16-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in treatment-naive or -experienced (standard or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon), genotype 3 patients without cirrhosis or with compensated cirrhosis. Among the 47 treatment-experienced participants with compensated cirrhosis who were treated for 16 weeks, the SVR12 was 96% (45/47). One of the virologic failures was a relapse and the other was a viral breakthrough. The patient with viral breakthrough had low serum DAA levels at week 4 of the study, suggesting poor adherence. The patient with relapse did not have baseline NS3 or NS5A RASs but did have dual NS5A RASs emerge at the time of failure (Wyles, 2018). Sixteen weeks of glecaprevir/pibrentasvir is a recommended regimen for peginterferon/ribavirin-experienced patients with cirrhosis and genotype 3 given the high SVR and lack of need for the addition of ribavirin to the regimen.

### Sofosbuvir/Velpatasvir/Voxilaprevir

The efficacy of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) in
genotype 3 patients is supported by the phase 3 POLARIS trials, which investigated 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in DAA-naive patients and 12 weeks in DAA-experienced patients. The 8-week regimen achieved a 96% SVR, which was noninferior to a 12-week sofosbuvir/velpatasvir regimen in the POLARIS-3 study, which included 35 interferon-experienced, cirrhotic patients with genotype 3 (Jacobson, 2017). Thus, this regimen is recommended in cirrhotic patients with genotype 3.

**Alternative Regimens**

**Elbasvir/Grazoprevir + Sofosbuvir**

The C-ISLE study evaluated the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir, with or without ribavirin, for 8 weeks to 16 weeks among treatment-naive or -experienced, genotype 3 patients with compensated cirrhosis. One hundred patients were enrolled, including 53 with a history peginterferon/ribavirin failure. Treatment-experienced participants were randomized to 12 weeks of elbasvir/grazoprevir plus sofosbuvir, 12 weeks of elbasvir/grazoprevir plus sofosbuvir and weight-based ribavirin, or 16 weeks of elbasvir/grazoprevir plus sofosbuvir (Foster, 2016b). All 3 arms had 100% SVR on the per protocol analysis, with 17 patients in each arm. The efficacy was high regardless of the presence of baseline RASs, including 3 patients with the Y93H substitution.

**Sofosbuvir/Velpatasvir + Ribavirin**

The phase 3 ASTRAL-3 study evaluated the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (without ribavirin) in 277 genotype 3 patients, including 71 with prior treatment experience and 80 with compensated cirrhosis (Foster, 2015a). Despite a high combined SVR12 of 95% (264/277), prior treatment (90% SVR12), Y93H substitution RAS (84% SVR12), and compensated cirrhosis (91% SVR12) had a moderate negative impact on treatment response. Among those with both compensated cirrhosis and prior treatment, the SVR12 was 89% (33/37). Similarly, in the POLARIS-3 study among peginterferon/ribavirin-experienced, cirrhotic genotype 3 patients treated for 12 weeks with sofosbuvir/velpatasvir, the SVR12 was 91% (29/32). (Jacobson, 2017).

The addition of ribavirin to the combination of sofosbuvir/velpatasvir was evaluated in genotype 3, cirrhotic patients (Esteban, 2018). In this study, 91% (92/101) of patients achieved SVR12 when treated with sofosbuvir/velpatasvir alone compared to 96% (99/103) of patients achieving SVR12 when ribavirin was added to the regimen. The largest benefit of the addition of ribavirin was seen in patients with baseline NS5A RAS with 84% (16/19) achieving SVR12 in the sofosbuvir/velpatasvir group compared to an SVR12 of 95% (21/22) in the sofosbuvir/velpatasvir plus ribavirin group. There were relatively small numbers of treatment-experienced patients enrolled in this study (27% overall). However, among the peginterferon/ribavirin-experienced patients, 93% (13/14) treated with sofosbuvir/velpatasvir achieved SVR12 whereas all 18 patients treated with sofosbuvir/velpatasvir plus ribavirin achieved SVR12.

Cirrhotic patients with genotype 3 and a prior non-DAA treatment failure are among the most difficult to treat. For this reason, ribavirin is recommended for all patients receiving sofosbuvir/velpatasvir, making this an alternative regimen.

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**Related References**

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