Peginterferon/Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

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<td>16 weeks</td>
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<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)</td>
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<td>Daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir (400 mg)</td>
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<sup>a</sup> For *decompensated cirrhosis*, please refer to the appropriate section.

<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

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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**Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection.** 

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**C-ISLE: Grazoprevir/Elbasvir plus Sofosbuvir in Treatment-naive and Treatment-experienced HCV GT3 Cirrhotic Patients Treated for 8, 12 or 16 weeks [Abstract 74].** In: *The Liver Meeting.* The Liver Meeting.; 2016.

Jacobson IM, Lawitz E, Gane EJ, et al. 
**Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials.** 

**Glecaprevir/pibrentasvir for hepatitis C virus genotype 3 patients with cirrhosis and/or prior treatment experience: a partially randomized phase 3 clinical trial: viral hepatitis.** 