DAA-Experienced (Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures), Genotype 3 Patients, With or Without Compensated Cirrhosis

(For glecaprevir/pibrentasvir treatment failures, please see that topic.)

Recommended regimens by evidence level for:

### Sofosbuvir + Ribavirin-Experienced (± Peginterferon), Genotype 3 Patients, With or Without Compensated Cirrhosis

- **RECOMMENDED**
  - Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)
    - DURATION: 12 weeks
    - RATING: I, B
  - Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)
    - DURATION: 16 weeks
    - RATING: IIb, B

  **a** For decompensated cirrhosis, please refer to the appropriate section.

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

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Recommended regimen for:

### DAA-Experienced (Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures), Genotype 3 Patients, With or Without Compensated Cirrhosis

- **RECOMMENDED**
  - Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)
    - DURATION: 12 weeks
    - RATING: I, A

  For patients with prior NS5A inhibitor failure and cirrhosis, addition of weight-based ribavirin is recommended.

  - DURATION: 12 weeks
    - RATING: Ila, C

  **a** For decompensated cirrhosis, please refer to the appropriate section.

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**Sofosbuvir/Velpatasvir/Voxilaprevir ± Ribavirin**
The phase 3 POLARIS-1 and POLARIS-4 trials included patients with genotype 3, without cirrhosis or with compensated cirrhosis, who had previously received a DAA regimen, with or without an NS5A inhibitor. The POLARIS-4 study included treatment-experienced patients who had previously received a DAA regimen but not an NS5A inhibitor. Participants were randomized to 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) (54 with genotype 3) or 12 weeks of sofosbuvir/velpatasvir (52 with genotype 3). SVR12 rates for the genotype 3 patients were 96% (52/54) and 85% (44/52), respectively. The 8 patients who experienced a relapse in the sofosbuvir/velpatasvir arm were primarily white males with compensated cirrhosis (7/8) and a high BMI (>25). Although none had baseline Y93H variants, all had emergence of Y93H variants at the time of relapse (Bourliere, 2017). Seven of 8 failures were treated previously with sofosbuvir plus ribavirin, with or without interferon. Thus, in contrast to genotype 2, sofosbuvir/velpatasvir is not recommended for retreatment of genotype 3 patients with prior exposure to sofosbuvir plus ribavirin, with or without interferon.

The POLARIS-1 study included patients who had previously received a regimen containing an NS5A inhibitor. Participants were randomized to 12 weeks of sofosbuvir/velpatasvir/voxilaprevir (78 with genotype 3) versus placebo. The SVR12 was 95% (74/78) for the genotype 3 patients. All 4 patients who experienced a relapse had cirrhosis (Bourliere, 2017). These data support the use of sofosbuvir/velpatasvir/voxilaprevir for 12 weeks in all DAA-experienced patients. In NS5A inhibitor-experienced genotype 3 patients with cirrhosis, however, the relapse rate is higher and adding weight-based ribavirin is recommended to minimize relapse risk.

**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 34 treatment-experienced participants with prior exposure to sofosbuvir who were treated for 16 weeks, regardless of cirrhosis status, SVR12 was 97% (33/34). The lone virologic failure was a relapse in a patient with cirrhosis. No NS5A RASs were present prior to treatment, however the L31F and Y93H substitutions were present at retreatment failure (Wyles, 2018). Sixteen weeks of glecaprevir/pibrentasvir is a recommended regimen for genotype 3 patients with prior exposure to sofosbuvir plus ribavirin given the high SVR and lack of need for addition of ribavirin to the regimen.

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**Related References**
