# Treatment-Naive Genotype 5 or 6

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

## Treatment-Naive Genotype 5 or 6 Patients With and Without Compensated Cirrhosis[a]

| RECOMMENDED | DURATION | RATING |
|---|---|---|
| Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg)[b] | 8 weeks (no cirrhosis) | I, A |
| | | |
| Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg)[b] | 12 weeks (cirrhosis) | I, A |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) | 12 weeks | I, B |
| Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) | 12 weeks | IIa, B |

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

## Recommended Regimens

### Glecaprevir/Pibrentasvir

Based on favorable data for 12 weeks of treatment for noncirrhotic patients in the phase 2 SURVEYOR-2 study (100% SVR12 in 34 patients with genotype 4, 5, or 6) (Kwo, 2017b), ENDURANCE-4 enrolled 121 DAA-naive or -experienced (sofosbuvir plus ribavirin ± peginterferon) genotype 4, 5, or 6 patients without cirrhosis to receive 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg pills (Asselah, 2018b). Of those enrolled, 86% had fibrosis stage F0 to F1 and 68% were treatment naive. The genotype distribution was 63% genotype 4, 21% genotype 5, and 16% genotype 6. The overall SVR12 rate for the intention-to-treat population was 99% (120/121), including 99% (75/76) for genotype 4, 100% for genotype 5 (26/26), and 100% (19/19) for genotype 6.

Genotype 4, 5, and 6 patients were not included in the randomized study to compare an 8-week vs 12-week course for DAA-naive, noncirrhotic patients. However, part 4 of the SURVEYOR-2 study investigated an 8-week course of glecaprevir/pibrentasvir in DAA-naive patients without cirrhosis (Asselah, 2018b). In the intention-to-treat analysis, 2/2 with genotype 5 and 9/10 with genotype 6 achieved SVR 12; there were no known virologic failures.

In addition, EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 99% (145/146) achieved SVR12, including 2/2 with genotype 5 and 7/7 with genotype 6 (Forns, 2017). Based on these studies, glecaprevir/pibrentasvir was approved for an 8-week course (noncirrhotic) and 12-week course (cirrhotic) of treatment for people with genotype 5 or genotype 6 infection.

## 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 5 and 6 infection in patients with and without cirrhosis (Feld, 2015). ASTRAL-1 included 24 genotype 5 treatment-naive participants with and without cirrhosis, 23 (96%) of whom achieved SVR12. The study also included 38 genotype 6 treatment-naive participants with and without cirrhosis, all of whom achieved SVR12 (100%). An additional 9 genotype 6 patients received sofosbuvir/velpatasvir in the POLARIS-2 phase 3 study, all of whom achieved SVR (Jacobson, 2017).

## Ledipasvir/Sofosbuvir

Although there are limited data on patients with genotype 5 infection, the in vitro activity of sofosbuvir and ledipasvir are quite good with $EC_{50}$ of 15 nM and 0.081 nM, respectively. Abergel and colleagues reported data from an open-label, single-arm study that included 41 genotype 5-infected patients with an overall SVR12 rate of 95% (39/41) (Abergel, 2016 ). The SVR12 rate was also 95% specifically in treatment-naive patients (20/21), of whom only 3 had cirrhosis but all achieved SVR12.

Ledipasvir has in vitro activity against most genotype 6 subtypes, except for 6e (Wong, 2013); (Kohler, 2014). A small, 2-center, open-label study (NCT01826981) investigated the safety and in vivo efficacy of ledipasvir/sofosbuvir for 12 weeks in treatment-naive and -experienced patients with genotype 6 infection. Twenty-five patients (92% were treatment-naive) who were primarily Asian (88%) had infection from 7 different subtypes (32% 6a; 24% 6e; 12% 6l; 8% 6m; 12% 6p; 8% 6q; 4% 6r). Two patients (8%) had cirrhosis. The SVR12 rate was 96% (24/25), and the single patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events (Gane, 2015).

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### Related References

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