# Treatment-Naive Genotype 4 With Compensated Cirrhosis

Recommended regimens listed by pangenotypic, evidence level, and alphabetically for:

## Treatment-Naive Persons With Genotype 4 Infection With Compensated Cirrhosis[a]

| RECOMMENDED | DURATION | RATING |
|---|---|---|
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) | 12 weeks | I, A |
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b] | 8 weeks[c] | I, B |
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) | 12 weeks | IIa, 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] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] For persons with HIV/HCV coinfection, a treatment duration of 12 weeks is recommended.

## 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 persons with or without cirrhosis. ASTRAL-1 included 64 treatment-naive participants with genotype 4 infection without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (100%) (Feld, 2015).

The POLARIS-2 phase 3 study randomized DAA-naive participants (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 participants with genotype 4 infection in the sofosbuvir/velpatasvir arm, 98% achieved SVR; 1 person experienced a relapse (Jacobson, 2017). A real-world, pooled analysis of 12 cohort studies demonstrated an SVR rate of 100% (38/38) among adults with genotype 4 infection and compensated cirrhosis who were treated with 12 weeks of sofosbuvir/velpatasvir (Mangia, 2020).

### Glecaprevir/Pibrentasvir

EXPEDITION-1 was a multicenter, open-label, single-arm, phase 3 trial that enrolled 146 treatment-naive or treatment-experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) participants with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. Participants 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, 99% (145/146) attained SVR12 (Forns, 2017). EXPEDITION-1 included 16 treatment-naive and treatment-experienced participants with genotype 4 infection and compensated cirrhosis. All 16 participants achieved SVR12. Baseline NS5A RASs were detected by next-generation sequencing (using a 15% detection cutoff) in 40% of 133 tested participants. Baseline NS5A RASs had no effect on SVR12 rates among treatment-naive and treatment-experienced participants with genotype 4 infection. Based on this study, a 12-week course of glecaprevir/pibrentasvir is recommended for treatment-naive persons with genotype 4 infection and compensated cirrhosis.

EXPEDITION-8 evaluated 8 weeks of glecaprevir/pibrentasvir among treatment-naive persons with compensated cirrhosis and genotype 1, 2, 4 (n=13), 5, or 6 infection. SVR12 rate was 99% with no virologic failures. Among participants with genotype 4 infection 100% (13/13) achieved SVR12 (Brown, 2020). People with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from the study.

### Elbasvir/Grazoprevir

In an integrated analysis of phase 2/3 trials, 15 treatment-naive persons with genotype 4 infection and cirrhosis were treated with 12 weeks of elbasvir/grazoprevir, with or without ribavirin, resulting in an SVR rate of 96% (Asselah, 2018c).

### Ledipasvir/Sofosbuvir

The SYNERGY trial was an open-label study evaluating 12 weeks of ledipasvir (90 mg)/sofosbuvir (400 mg) in 21 participants with genotype 4 infection, of whom 60% were treatment naive and 43% had advanced fibrosis (Metavir stage F3 or F4) (Kohli, 2015). One person took the first dose and then withdrew consent. The 20 participants 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. Another open-label, single-arm study evaluating 12 weeks of ledipasvir/sofosbuvir that included 22 treatment-naive participants with genotype 4 infection (1 with cirrhosis) reported an SVR12 rate of 95% (21/22) in this patient population (Abergel, 2016).

### Related References

Abergel A, Metivier S, Samuel D, et al. **Ledipasvir plus sofosbuvir for 12 weeks in patients with hepatitis C genotype 4 infection**. *Hepatology*. 2016;64(4):1049-1056.

Asselah T, Reesink H, Gerstoft J, et al. **Efficacy of elbasvir and grazoprevir in participants with hepatitis C virus genotype 4 infection: a pooled analysis**. *Liver Int*. 2018;38(9):1583-1591.

Brown RS, Hézode C, Wang S, et al. **Preliminary efficacy and safety of 8-week glecaprevir/pibrentasvir in patients with HCV genotype 1-6 infection and compensated cirrhosis: the EXPEDITION-8 study [Abstract LB-7]**. Presented at: The Liver Meeting; November 9-13, 2018; San Francisco, California.

Brown RS Jr, Buti M, Rodrigues L, et al. Glecaprevir/pibrentasvir for 8 weeks in treatment-naive patients with chronic HCV genotypes 1-6 and compensated cirrhosis: the EXPEDITION-8 trial. *J Hepatol*. 2020;72(3):441-449. doi: 10.1016/j.jhep.2019.10.020.

Feld JJ, Jacobson IM, Hézode C, et al. **Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection**. *N Engl J Med*. 2015;373(27):2599-2607.

Forns X, Lee SS, Valdes J, et al. **Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (EXPEDITION-1): a single-arm, open-label, multicentre phase 3 trial**. *Lancet Infect Dis*. 2017;17(10):1062-1068.

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**. *Gastroenterology*. 2017;153(1):113-122.

Kohli A, Kapoor R, Sims Z, et al. **Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study**. *Lancet Infect Dis*. 2015;15(9):1049-1054.

Mangia A, Milligan S, Khalili M, et al. **Global real-world evidence of sofosbuvir/velpatasvir as simple, effective HCV treatment: analysis of 5552 patients from 12 cohorts**. *Liver Int*. 2020;40(8):1841-1852.

**Additional Reading**

- Persons With HIV/HCV Coinfection
- Persons With Renal Impairment
- Management of Acute HCV Infection

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