Treatment-Naive Genotype 5 or 6

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

Treatment-Naive Persons With Genotype 5 or 6 Infection, With and Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A[c]
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)[d]	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 compensated cirrhosis, rating is I, B.
[d] Not recommended for genotype 6e if subtype is known.

Recommended Regimens

Glecaprevir/Pibrentasvir

Based on favorable data for 12 weeks of treatment for persons without cirrhosis in the phase 2 SURVEYOR-2 study (100% SVR12 rate in 34 participants with genotype 4, 5, or 6) (Kwo, 2017b), ENDURANCE-4 enrolled 121 DAA-naive or DAA-experienced (sofosbuvir plus ribavirin ± peginterferon) participants with genotype 4, 5, or 6 infection 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.

People with genotype 4, 5, or 6 infection were not included in the randomized study to compare an 8-week course with a 12-week course of glecaprevir/pibrentasvir for DAA-naive persons without cirrhosis. However, part 4 of the SURVEYOR-2 study investigated an 8-week course of glecaprevir/pibrentasvir in DAA-naive persons without cirrhosis (Asselah, 2018b). In the intention-to-treat analysis, 100% (2/2) with genotype 5 infection and 90% (9/10) with genotype 6 infection achieved SVR12; there were no known virologic failures. Further, ENDURANCE-5,6 was a phase 3b, single-arm, open-label, multicenter study of the efficacy of glecaprevir/pibrentasvir among DAA-naive persons with genotype 5 (n=23) or 6 (n=61) infection. Participants without cirrhosis received an 8-week regimen; those with cirrhosis (11% of participants) received 12 weeks of treatment (Asselah, 2019). Overall SVR rate was 98% with 2 virologic failures. Treatment failed in a participant with genotype 6f infection and cirrhosis, and in another with genotype 5a infection without cirrhosis.

In addition, EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir in DAA-naive (75%) or DAA-experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) persons with compensated cirrhosis. The participants with genotype 1, 2, 4, 5, or 6 infection were given 12 weeks of glecaprevir/pibrentasvir; 99% (145/146) attained SVR12, including 100% (2/2) with genotype 5 infection and 100% (7/7) with genotype 6 infection (Forns, 2017). Based on these studies, glecaprevir/pibrentasvir was approved for an 8-week course (those without cirrhosis) and 12-week course (those with cirrhosis) of treatment for people with genotype 5 or 6 infection.

EXPEDITION-8 evaluated 8 weeks of glecaprevir/pibrentasvir among treatment-naive persons with compensated cirrhosis and genotype 1, 2, 4, 5 (n=1) or 6 (n=9) infection. Overall SVR12 rate was 99% with no virologic failures. SVR rate was 100% (1/1) for genotype 5 infection as well as genotype 6 infection (9/9) (Brown, 2020). People with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from the study.

An integrated analysis glecaprevir/pibrentasvir treatment response among the 181 participants with genotype 5 or 6 infection from phase 2/3 studies (including those discussed above) showed comparable response rates between 8 weeks and 12 weeks of treatment with no signal of poorer performance among persons with cirrhosis with an 8-week regimen (Yao, 2020).

Sofosbuvir/Velpatasvir

Twelve weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) was approved by the FDA for the treatment of genotype 5 and 6 infection in persons with and without cirrhosis (Feld, 2015). ASTRAL-1 included 24 treatment-naive participants with genotype 5 infection, with or without cirrhosis, 96% (23/24) of whom achieved SVR12. The study also included 38 treatment-naive participants with genotype 6 infection, with or without cirrhosis, all of whom attained SVR12. An additional 9 persons with genotype 6 infection received sofosbuvir/velpatasvir in the POLARIS-2 phase 3 study, all of whom achieved SVR (Jacobson, 2017).

Two real-world cohort studies evaluated 12 weeks of sofosbuvir/velpatasvir among predominantly treatment-naive persons with genotype 6 infection. SVR rate was 100% in a cohort of persons (n=23) from Southwest China, none of whom had clinical cirrhosis (Wu, 2019). SVR rate was also 100% in a cohort of predominantly Vietnamese adults (n=43) residing in the United States, 12% of whom had cirrhosis (Nguyen, 2019). A real-world, pooled analysis of 12 cohorts that evaluated adults treated with 12 weeks of sofosbuvir/velpatasvir demonstrated an SVR rate of 98.5% (67/68) among participants with genotype 5 or 6 infection; all 13 participants with compensated cirrhosis attained SVR (Mangia, 2020).

Ledipasvir/Sofosbuvir

Although there are limited data on persons with genotype 5 infection, the in-vitro activity of sofosbuvir and ledipasvir are quite good with EC50 of 15 nM and 0.081 nM, respectively. An open-label, single-arm study that included 41 participants with genotype 5 infection demonstrated an overall SVR12 rate of 95% (39/41) (Abergel, 2016). The SVR12 rate was also 95% (20/21) specifically among treatment-naive participants, 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 investigated the safety and in vivo efficacy of ledipasvir/sofosbuvir for 12 weeks among treatment-naive and treatment-experienced persons with genotype 6 infection. Twenty-five participants (92% 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 participants (8%) had cirrhosis. The SVR12

rate was 96% (24/25), and the single person who experienced relapse had discontinued therapy at week 8 because of drug use. No participants discontinued treatment owing to adverse events (Gane, 2015).

In the largest US study, 60 persons with genotype 6 infection were randomized to 8 weeks (treatment-naive, no cirrhosis) or 12 weeks (treatment-naive or treatment-experienced, with or without cirrhosis) of ledipasvir/sofosbuvir; SVR rate was 95% in both treatment groups (Nguyen, 2017). A real-world cohort of 92 treatment-naive persons with genotype 6 infection (predominantly Vietnamese persons residing in the United States, 51% with cirrhosis) was treated with 12 weeks of ledipasvir/sofosbuvir; SVR12 rate was 96.6% (Nguyen, 2019). Subtype data were not available.

A systematic review that examined the response to DAA therapy among persons with genotype 6 infection highlighted the heterogeneity of SVR rates in response to ledipasvir/sofosbuvir treatment across Asian countries (64% in Myanmar compared with 100% in Vietnam) (Mettikanont, 2019). The reasons for these differences are likely multiple; the variable distribution of subtypes within the populations is a potential explanation. Pending more data, a conservative approach is recommended for persons with subtype 6e infection who are best treated with an alternative regimen.

Related References

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Additional Reading

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

Last Update: October 24, 2022 **Last Review:** January 15, 2025