

NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients With Compensated Cirrhosis

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

NS3 Protease Inhibitor (Telaprevir, Boceprevir, or Simeprevir) + Peginterferon/Ribavirin Treatment-Experienced, Genotype 1 Patients 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	12 weeks	IIa, B
ALTERNATIVE	DURATION	RATING 
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for all genotype 1b patients, and genotype 1a patients without baseline NS5A RASs ^c for elbasvir	12 weeks	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for genotype 1a patients with baseline NS5A RASs ^c for elbasvir	16 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 Includes genotype 1a RASs at amino acid position 28, 30, 31, or 93 known to confer [antiviral resistance to elbasvir](#). Baseline testing for these RASs is recommended for patients receiving elbasvir/grazoprevir-based regimens.

Recommended Regimens

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks ([Feld, 2015](#)). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1 treatment-experienced patients was 99.1% (109/110), with 100% (78/78) in patients

with genotype 1a and 96.9% (31/32) among those with genotype 1b. In this study, 100% (48/48) of participants who previously experienced treatment failure with a protease inhibitor plus peginterferon/ribavirin achieved SVR12 ([Feld, 2015](#)). These data are supported by similarly high SVR12 rate seen in a preceding phase 2, open-label trial wherein 100% (27/27) of patients with the same type of treatment failure history achieved SVR12 with 12 weeks of sofosbuvir/velpatasvir therapy ([Pianko, 2015](#)).

Glecaprevir/Pibrentasvir

In parts 1 and 2 of the MAGELLAN-1 trial, 42 genotype 1 patients had been previously treated with either an NS5A inhibitor or a protease inhibitor. Twenty-four percent of these patients had cirrhosis. Among those previously treated with NS3/4A protease inhibitor-based therapy (includes simeprevir, boceprevir, or telaprevir without NS5A inhibitor exposure) who were retreated with 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, 92% (23/25) achieved SVR12. Simeprevir plus sofosbuvir failures were included. Of the 2 patients who did not achieve SVR, neither experienced virologic failure ([Poordad, 2017](#)); ([Poordad, 2017b](#)).

Alternative Regimens

Ledipasvir/Sofosbuvir + Ribavirin

The ION-2 trial evaluated the safety and efficacy of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in genotype 1 patients in whom prior treatment with an HCV protease inhibitor (telaprevir or boceprevir) plus peginterferon/ribavirin failed ([Afdhal, 2014b](#)). SVR12 with 12 weeks of therapy was 94%. Relapse rates were numerically higher in the 12-week treatment arms than in the 24-week arms. The pretreatment presence of cirrhosis and/or NS5A RASs were the major reasons for the higher relapse rate in the 12-week arm. Thus, genotype 1 patients without cirrhosis in whom a prior regimen of peginterferon/ribavirin plus an HCV protease inhibitor failed should receive ledipasvir/sofosbuvir plus weight-based ribavirin for 12 weeks to optimize treatment response ([Bourliere, 2015](#)). Due to the need for ribavirin, this is recommended as an alternative regimen.

Elbasvir/Grazoprevir + Ribavirin

Grazoprevir is a next-generation HCV NS3/4A protease inhibitor that retains activity in vitro against many common protease inhibitor RASs ([Summa, 2012](#)); ([Howe, 2014](#)). Elbasvir is an HCV NS5A inhibitor. The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with expanded weight-based ribavirin (800 mg to 1400 mg) was evaluated in an open-label, phase 2 study of 79 patients who experienced a prior treatment failure with interferon-based therapy plus a protease inhibitor ([Forns, 2015a](#)). Most enrolled participants had a prior treatment failure with peginterferon/ribavirin plus either boceprevir (35%, n=28) or telaprevir (54%, n=43). Importantly, 83% of enrolled patients had experienced virologic failure with their prior protease inhibitor-containing regimen and 44% had detectable NS3 RASs to early-generation protease inhibitors at study entry. SVR12 was attained in 96% of patients, including 93% (28/30) of genotype 1a patients and 94% (32/34) of those with cirrhosis. Baseline NS3 RASs did not appear to have a large impact on treatment response with an SVR12 of 91% (31/34). Presence of NS5A or dual NS3/NS5A substitutions was associated with lower SVR12 rates of 75% and 66%, respectively. But with only 3 failures in the entire study, firm conclusions cannot be drawn.

Consistent with recommendations for other populations, extension of therapy to 16 weeks with ribavirin is recommended for patients with baseline NS5A RASs resulting in a >5-fold shift in elbasvir potency. Due to the need for ribavirin, both the 12-week and 16-week course of therapy are recommended as alternative regimens.

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Related References

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