

## NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients Without Cirrhosis

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

### NS3 Protease Inhibitor (Telaprevir, Boceprevir, or Simeprevir) + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
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) <sup>a</sup>	12 weeks	IIa, B
ALTERNATIVE	DURATION	RATING 
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 RAS <sup>b</sup> 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 RAS <sup>b</sup> for elbasvir	16 weeks	IIa, B

<sup>a</sup> This is a 3-tablet coformulation. Please refer to the prescribing information.

<sup>b</sup> Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer [antiviral resistance](#).

## Recommended Regimens

### Ledipasvir/Sofosbuvir

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-infected patients in whom prior treatment with an HCV protease inhibitor (telaprevir or boceprevir) plus peginterferon/ribavirin failed ([Afdhal, 2014b](#)). SVR12 rates with the 12-week and 24-week ledipasvir/sofosbuvir regimens were 94% and 98%, respectively. Relapse rates were numerically higher with the 12-week regimen versus the 24-week regimen. The presence of cirrhosis and/or baseline NS5A RASs were the major reasons for the higher relapse rate in the 12-week study arm. Thus, genotype 1-infected patients without cirrhosis in whom a prior regimen of peginterferon/ribavirin plus an HCV protease inhibitor failed can receive a 12-week course of ledipasvir/sofosbuvir.

## Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naïve or -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks ([Feld, 2015](#)). 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 SVR rates 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-infected 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 protease inhibitor-based therapy (which 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

### Elbasvir/Grazoprevir + Ribavirin

Grazoprevir is a next-generation HCV NS3/4A protease inhibitor that retains activity in vitro against many common protease inhibitor resistant substitutions ([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 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 in 93% (28/30) of genotype 1a-infected patients and 94% (32/34) in those with cirrhosis. Baseline NS3 RASs did not appear to have a large impact on treatment response with an SVR12 rate 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, a 12-week course of elbasvir/grazoprevir is a recommended regimen for patients with genotype 1a infection and no baseline NS5A RASs. Extension of therapy to 16 weeks plus weight-based ribavirin is an alternative treatment option for genotype 1a-infected patients with baseline NS5A RASs resulting in a >5-fold shift in elbasvir potency.

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**Related References**

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