

## Peginterferon/Ribavirin-Experienced, Genotype 1b Patients Without Cirrhosis

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

### Peginterferon/Ribavirin-Experienced, Genotype 1b Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>a</sup>	8 weeks	I, A
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
ALTERNATIVE	DURATION	RATING 
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg)	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg) <sup>b</sup> plus sofosbuvir (400 mg)	12 weeks	I, B

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

<sup>b</sup> The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on [HIV/HCV coinfection](#) for patients on antiretroviral therapy.

## Recommended Regimens

### Elbasvir/Grazoprevir

The phase 3 C-EDGE TE trial evaluated the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) in patients with a prior peginterferon/ribavirin treatment failure. Patients were randomized to elbasvir/grazoprevir for 12 weeks or 16 weeks, with or without ribavirin. Genotype 1-infected patients treated for 12 weeks without ribavirin had an overall SVR12 rate of 93.8% (90/96), which was nearly identical to the response rate in patients treated for 12 weeks with added ribavirin (94.4%, 84/89) ([Kwo, 2017](#)). SVR rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week elbasvir/grazoprevir regimen. In genotype 1a-infected patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a-infected patients with baseline NS5A RASs (>5 fold), only 52% (11/21) achieved SVR due to a higher relapse rate ([Kwo, 2015](#)).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR rate in treatment-experienced, genotype 1a-infected patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) ([Zeuzem, 2017](#)). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR, compared to 96% (52/54) among those without these baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen with the 12-week regimen ([Jacobson, 2015b](#)).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended for genotype 1a-infected patients being considered for elbasvir/grazoprevir therapy. If these RASs are present, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [ $<75$  kg] to 1200 mg [ $\geq 75$  kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

## Glecaprevir/Pibrentasvir

The phase 3 ENDURANCE-1 trial enrolled 703 treatment-naïve or -experienced patients (interferon or peginterferon  $\pm$  ribavirin, or sofosbuvir plus ribavirin  $\pm$  peginterferon) with genotype 1 infection without cirrhosis. Participants were randomized to 8 weeks or 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills ([Zeuzem, 2016](#)). Of those enrolled, 43% had genotype 1a infection, 85% had fibrosis stage F0 or F1, and 38% were treatment experienced. Ninety-nine percent of the treatment-experienced patients had previously received interferon-based therapy and 1% had received sofosbuvir-based treatment. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority. A single patient experienced on-treatment virologic failure (genotype 1a, day 29). There were no documented relapses in either study arm. This regimen was well tolerated with rare adverse events leading to discontinuation (0.1%); no significant laboratory abnormalities were noted.

## Ledipasvir/Sofosbuvir

The daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) has been evaluated in patients without cirrhosis and a history of treatment failure with peginterferon/ribavirin, with or without HCV protease inhibitors (telaprevir or boceprevir). In the ION-2 study, patients who had not responded to prior peginterferon/ribavirin therapy were treated with ledipasvir/sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In the population without cirrhosis, the overall SVR rate was 98%. Specifically, in patients without cirrhosis and a history of peginterferon/ribavirin failure, 94% (33/35) achieved SVR after 12 weeks of ledipasvir/sofosbuvir treatment, and 100% (38/38) achieved SVR in the ledipasvir/sofosbuvir plus ribavirin study arm ([Afdhal, 2014b](#)). This regimen was well tolerated in all groups with no serious adverse events reported for the 12-week regimen, with or without ribavirin.

## 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 who were treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination 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-infected, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a infection and 97% (31/32) in those with genotype 1b infection. Among

patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b-infected, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. The regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) vs the placebo group (77%).

## Alternative Regimens

### Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

In the SAPPHERE-2 study, the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin was investigated for the treatment of patients with genotype 1 infection in whom previous peginterferon/ribavirin therapy failed ([Zeuzem, 2014](#)). In this phase 3 trial, patients without cirrhosis who were treated for 12 weeks had an overall SVR rate of 96% (286/297). Response rates did not differ substantially when stratified by subtype (genotype 1a, 96% [166/173]; genotype 1b, 97% [119/123]) or kinetics of prior response to peginterferon/ribavirin (relapse, 95% [82/86]; partial response, 100% [65/65]; null response, 95% [139/146]).

In the PEARL-II study, 179 genotype 1b-infected patients without cirrhosis in whom previous peginterferon/ribavirin therapy failed were treated for 12 weeks with paritaprevir/ritonavir/ombitasvir plus dasabuvir, with or without weight-based ribavirin ([Andreone, 2014](#)). The SVR rates were 100% (91/91) in the ribavirin-free arm and 97% (85/88) in the ribavirin-containing arm, supporting the recommendation that this regimen may be used without ribavirin for patients with genotype 1b infection. Due to the complexity of this regimen—which is primarily driven by the need to include weight-based ribavirin for some patients and the drug interaction profile—it is categorized as an alternative regimen, suggesting it remains highly effective but with limitations.

### Simeprevir + Sofosbuvir

The phase 3 OPTIMIST-1 study evaluated a 12-week course of daily simeprevir (150 mg) plus sofosbuvir (400 mg) in genotype 1-infected patients who were treatment-naïve or -experienced without cirrhosis ([Kwo, 2016](#)). Patients were randomized to 8 weeks or 12 weeks of treatment. Superiority in SVR12 was assessed for 12 weeks of simeprevir plus sofosbuvir versus a composite historical control SVR rate. SVR12 in the 12-week arm was 97%, meeting superiority versus the historical control (87%). However, the 8-week arm only achieved an SVR12 rate of 83%, which did not meet superiority versus the historical control. Among those treated for 12 weeks, the SVR rate in peginterferon/ribavirin-experienced patients was 95% (38/40). The SVR rate in patients with genotype 1a infection with a baseline Q80K substitution (96%; 44/46) was similar to that observed in patients without the substitution (97%; 68/70). Although simeprevir plus sofosbuvir is a highly effective regimen, the drug interaction profile with simeprevir and the complexity of accessing this regimen (a combination of 2 different manufacturer's products) makes it an alternative regimen.

### Daclatasvir + Sofosbuvir

Two observational, early access programs in the United Kingdom and France have studied the daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) in genotype 1-infected, treatment-experienced patients with a history of peginterferon/ribavirin treatment failure ([Foster, 2015](#)); ([Pol, 2017](#)); ([Foster, 2016](#)). In the French cohort, patients were treated with daclatasvir plus sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In patients treated with daclatasvir plus sofosbuvir alone, a numerically higher rate of sustained virologic response at 4 weeks (SVR4) was seen in those treated for 24 weeks (12 weeks, 82.6% [15/18] vs 24 weeks, 96.1% [75/78]). Patients treated with daclatasvir and sofosbuvir plus ribavirin had high response rates in the 12-week and 24-week treatment groups (100% and 97.1%, respectively)—but only 4 patients were treated for 12 weeks. The selection of daclatasvir or ledipasvir and the use of ribavirin were at the discretion of the treating physician; most patients (94.4%) had ribavirin in their regimen. Among patients treated with sofosbuvir plus ribavirin for 12 weeks, the SVR rates were 86% for those who received ledipasvir (n=164) and 82% for those who received daclatasvir (n=82).

Based on these limited data, consideration should be given to the addition of ribavirin when working with more difficult-to-treat patients, such as those with compensated cirrhosis. Due to the complexity of accessing this regimen (a combination of 2 different manufacturer's products), this is recommended as an alternative regimen.

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