

## Peginterferon/Ribavirin-Experienced, Genotype 1a Patients With Compensated Cirrhosis

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

### Peginterferon/Ribavirin-Experienced, Genotype 1a Patients With Compensated Cirrhosis<sup>a</sup>

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs <sup>b</sup> for elbasvir	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>c</sup>	12 weeks	I, 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 patients with baseline NS5A RASs <sup>b</sup> for elbasvir	16 weeks	I, B

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

<sup>b</sup> Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer [antiviral resistance](#). Baseline testing for these RASs is recommended for patients receiving elbasvir/grazoprevir-based regimens.

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

## Recommended Regimens

### Elbasvir/Grazoprevir

The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) was evaluated in patients with a history of failed peginterferon/ribavirin therapy in the C-EDGE TE study. In this phase 3 trial, patients were randomized to 12 weeks or 16 weeks of elbasvir/grazoprevir, with or without ribavirin. Genotype 1-infected patients treated for 12 weeks without ribavirin had an overall SVR 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](#)). Response rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96). A subset analysis of patients with compensated cirrhosis revealed similar response rates to the population without cirrhosis when treated with elbasvir/grazoprevir without ribavirin for 12 weeks (SVR with cirrhosis 95% [19/20]; SVR without cirrhosis 94.9% [37/39]).

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 52.4% (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 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 in 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.

## Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naïve and -experienced patients with genotype 1, 2, 4, 5, or 6 infection 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. This regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) versus the placebo group (77%).

## Glecaprevir/Pibrentasvir

The EXPEDITION-1 trial investigated use of 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 in 146 patients with compensated cirrhosis infected with genotype 1, 2, 4, 5, or 6. Twenty-five percent (36/146) of enrolled patients were non-DAA treatment experienced. SVR12 was 98.9% (89/90) among genotype 1-infected patients. The single treatment failure occurred in a patient with genotype 1a infection who relapsed at post-treatment week 8 ([Forns, 2017](#)). Ninety-one percent of patients (133/146) had a Child-Pugh score of 5 and 9% (13/146) had a Child-Pugh score of 6. Twenty percent of patients had a platelet count  $<100 \times 10^9/L$  and all but 1 participant had a normal albumin level. In this patient population with compensated cirrhosis, the regimen was safe and well tolerated. There were 11 serious adverse events; none were DAA-related and no adverse events led to discontinuation of the study drugs. Glecaprevir/pibrentasvir is a safe and highly efficacious 12-week regimen in patients with well-compensated cirrhosis.

## Alternative Regimens

### Ledipasvir/Sofosbuvir + Ribavirin

The double-blind, placebo-controlled, phase 2 SIRIUS trial enrolled genotype 1-infected patients with compensated

cirrhosis who did not achieve SVR with peginterferon/ribavirin plus telaprevir or boceprevir. Participants were randomized to either 12 weeks of placebo followed by 12 weeks of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin, or ledipasvir/sofosbuvir plus placebo for 24 weeks. The SVR rates were similar in the study arms: 96% (74/77) in the group that received ledipasvir/sofosbuvir plus ribavirin for 12 weeks (3 relapses), and 97% (75/77) in the group that received ledipasvir/sofosbuvir for 24 weeks (2 relapses) ([Bourliere, 2015](#)).

These findings are further supported by a post hoc analysis of treatment-naïve or -experienced, genotype 1-infected patients with compensated cirrhosis who were treated with ledipasvir/sofosbuvir in phase 2 and phase 3 studies (including the SIRIUS trial). In this analysis, ledipasvir/sofosbuvir for 12 weeks was inferior to ledipasvir/sofosbuvir plus ribavirin for 12 weeks. Safety and tolerability were similar in the groups and, apart from anemia, reported adverse events did not differ substantially between patients treated with or without ribavirin ([Reddy, 2015](#)). Due to the need for ribavirin, this regimen is recommended as an alternative for genotype 1-infected patients with a history of peginterferon/ribavirin failure who have compensated cirrhosis.

Baseline NS5A RASs adversely impact response to ledipasvir/sofosbuvir therapy. The magnitude of impact varies based on several factors, including virus (genotype subtype, specific RAS); regimen (companion drugs, use of ribavirin); and patient factors (treatment experience, presence of cirrhosis). In an analysis of more than 350 genotype 1-infected, treatment-experienced patients with cirrhosis, the presence of baseline ledipasvir RASs (defined as RASs resulting in a >2.5-fold shift in ledipasvir EC<sub>50</sub>) detected at a 1% level resulted in a lower SVR12 rate compared to those without baseline RASs ([Zeuzem, 2017](#)). The SVR12 rates were 89% with RASs versus 96% in the absence of RASs with a 12-week course of ledipasvir/sofosbuvir plus ribavirin, and 87% versus 100%, respectively, with a 24-week course of ledipasvir/sofosbuvir without ribavirin. The impact of baseline RASs is likely greater in a genotype 1a only population.

Given the vulnerable nature of this population, baseline NS5A resistance testing should be considered for genotype 1a-infected, treatment-experienced patients with compensated cirrhosis prior to use of ledipasvir/sofosbuvir. If ledipasvir-associated RASs are detected, a different regimen should be used to optimize treatment response.

## Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

The TURQUOISE-III study evaluated the safety and efficacy of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) without ribavirin for 12 weeks in patients with genotype 1b infection and compensated cirrhosis. Sixty patients were enrolled (62% men; 55% treatment experienced; 83% with the IL28B non-CC genotype; 22% with a platelet count <90 x 10<sup>9</sup>/L; and 17% with an albumin level <3.5 g/dL). All patients completed treatment and achieved SVR12 ([Feld, 2016](#)). Based on this study, treating patients with genotype 1b infection with paritaprevir/ritonavir/ombitasvir plus dasabuvir without ribavirin is ranked as an alternative regimen (primarily because of drug interactions), regardless of prior treatment experience or the presence of compensated cirrhosis.

The US Food and Drug Administration (FDA) released a [warning](#) in October 2015 regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis. (This statement is based on our review of the limited data available from the FDA and will be updated if and when more data become available.)

Paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with Child-Turcotte-Pugh (CTP) class B or class C hepatic impairment (decompensated liver disease). The manufacturer's pharmacovigilance program reported the rapid onset of liver injury and, in some cases, hepatic decompensation in patients with cirrhosis—including CTP class A compensated cirrhosis and decompensated cirrhosis—who were receiving paritaprevir/ritonavir/ombitasvir ± dasabuvir. The liver injury and decompensating events occurred largely during the first 4 weeks of therapy and primarily involved a rapid increase in total and direct bilirubin, often associated with a concomitant increase in liver enzyme levels. In most cases, early recognition and prompt discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir resulted in resolution of the hepatic injury. However, some patients (including at least 2 persons with CTP class A compensated cirrhosis) died or required liver transplantation. Although cirrhosis carries a 2% to 4% annual risk of hepatic decompensation, the rapid onset of hepatic decompensation and, in many cases, its resolution with discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir suggest drug-induced liver injury. Although paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with CTP class B or class C cirrhosis and decompensated liver disease, predictors of these events in patients with CTP class A cirrhosis are currently unclear.

For patients with CTP class A cirrhosis, the unlikely but real possibility of drug-induced liver injury should be discussed with the patient. If the decision is made to initiate treatment with paritaprevir/ritonavir/ombitasvir ± dasabuvir, close monitoring of total and direct bilirubin and transaminase levels every 1 to 2 weeks for the first 4 weeks of therapy is recommended to ensure early detection of drug-induced liver injury. Educating patients about the importance of reporting systemic symptoms, such as jaundice, weakness, and fatigue, is also strongly recommended. The regimen should be discontinued immediately if drug-induced liver injury is suspected. If a patient is already taking paritaprevir/ritonavir/ombitasvir ± dasabuvir and tolerating the regimen, laboratory monitoring as noted without discontinuation of treatment is recommended unless there are signs or symptoms of liver injury. If heightened monitoring cannot be provided during the first 4 weeks of therapy with paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with compensated cirrhosis, use of these regimens is not recommended.

**Last update:** May 24, 2018

### Related References

- Bourliere M, Bronowicki J, de Ledinghen V, et al. [Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial \(SIRIUS\)](#). *Lancet Infect Dis*. 2015;15(4):397-404.
- 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.
- Feld JJ, Moreno C, Trinh R. [Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12 weeks](#). *J Hepatol*. 2016;64(2):301-307.
- 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, Asante-Appiah E, Wong P, et al. [Prevalence and impact of baseline NSA resistance associated variants \(RAVs\) on the efficacy of elbasvir/grazoprevir \(EBR/GZR\) against GT1a infection \[abstract LB-22\]](#). *The Liver Meeting*. 2015.
- Kwo PY, Gane EJ, Peng C-Y, et al. [Efficacy and safety of grazoprevir/elbasvir +/- RBV for 12 weeks in patients with HCV G1 or G4 infection who previously failed peginterferon/RBV: C-EDGE treatment-experienced trial \[P0886\]](#). *J Hepatol*. 2015;62(Suppl 2):S674-S675.
- Kwo PY, Gane EJ, Peng CY, et al. [Effectiveness of elbasvir and grazoprevir combination, with or without ribavirin, for treatment-experienced patients with chronic hepatitis C infection](#). *Gastroenterology*. 2017;152(1):164-175.e4.
- Reddy KR, Bourliere M, Sulkowski MS, et al. [Ledipasvir and sofosbuvir in patients with genotype 1 hepatitis C virus infection and compensated cirrhosis: An integrated safety and efficacy analysis](#). *Hepatology*. 2015;[Ahead of print].
- Zeuzem S, Mizokami M, Pianko S, et al. [NS5A resistance-associated substitutions in patients with genotype 1 hepatitis C virus: Prevalence and effect on treatment outcome](#). *J Hepatol*. 2017;66(5):910-918.