



Treatment-Naive Genotype 1a With Compensated Cirrhosis

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

Treatment-Naive Genotype 1a 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 | 8 weeks | I, B |
| Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) | 12 weeks | I, A |
| ALTERNATIVE | DURATION | RATING  |
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) | 12 weeks | I, A |

^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.

For genotype 1a-infected, treatment-naive patients with compensated cirrhosis, there are 3 recommended regimens with comparable efficacy.

Recommended Regimens

Sofosbuvir/Velpatasvir

The daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 who were treatment naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201) ([Feld, 2015](#)). Of the 328 genotype 1 patients included, 323 achieved SVR12 with no difference in SVR12 observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR12 (99%).

The presence of baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR12 rate for genotype 1 ([Hézode, 2018](#)). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotype 1, 2, 3, 4, 5, or 6—19% of whom had

cirrhosis—to receive 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir ([Jacobson, 2017](#)). Of participants treated with sofosbuvir/velpatasvir, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed with each subtype. A real-world, pooled analysis of 12 cohort studies demonstrated an SVR of 98.3% (349/355) among adults with genotype 1 and compensated cirrhosis who were treated with 12 weeks of sofosbuvir/velpatasvir ([Mangia, 2020](#)).

Glecaprevir/Pibrentasvir

EXPEDITION-1 investigated the 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 in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 145 (99%) achieved SVR12. The single relapse occurred in a genotype 1a patient; SVR12 among these patients was 98% (47/48) ([Forns, 2017](#)).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected adults with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 rate was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection ([Rockstroh, 2018](#)). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

EXPEDITION-8 evaluated glecaprevir/pibrentasvir for a reduced duration of 8 weeks in 280 treatment-naive patients with compensated cirrhosis and genotype 1 (n=95, genotype 1a), 2, 4, 5 or 6 infection. Patients with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from this study. SVR12 was 99% with no virologic failures ([Brown, 2018](#)).

Ledipasvir/Sofosbuvir

The fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on two registration trials: ION-1 (865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin ([Afdhal, 2014a](#)). SVR12 rates were 97% to 99% across all study arms with no difference in SVR12 based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%).

Alternative Regimen

Elbasvir/Grazoprevir

The recommendation for use of daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) in cirrhotic patients with genotype 1 infection is based on 92 patients (22% of the study cohort) in the phase 3 C-EDGE trial who had Metavir F4 disease ([Zeuzem, 2015f](#)). SVR12 was 97% in this subgroup of cirrhotic patients. A similar 97% (28/29) SVR12 rate had previously been demonstrated in genotype 1 cirrhotic treatment-naive patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase 2 C-WORTHY trial, which enrolled both HCV-monoinfected and HIV/HCV-coinfected patients ([Lawitz, 2015c](#)). Presence or absence of cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen ([Zeuzem, 2017](#)); ([Lawitz, 2015c](#)).

Presence of certain baseline NS5A RASs significantly reduces SVR12 rates with a 12-week course of the elbasvir/grazoprevir regimen in genotype 1a-infected patients ([Zeuzem, 2017](#)). Baseline NS5A RASs were identified in 12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study, of which 58% (11/19) achieved SVR12 compared to 99% (133/135) in patients without these RASs ([Zeuzem, 2017](#)). Among treatment-naive patients, the presence of baseline NS5A RASs with a >5-fold reduced sensitivity to elbasvir was associated with the most significant reduction in SVR12 with only 22% (2/9) of genotype 1a patients with these RASs achieving SVR12.

Recommendations for prolonging duration of treatment to 16 weeks with inclusion of ribavirin for treatment-naive genotype 1a patients with baseline NS5A RASs are based on extrapolation of data from the C-EDGE TE trial. In this phase 3 open-label trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, among 58 genotype 1a patients who received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, there were no virologic failures ([Kwo, 2017](#)). Subsequent integrated analysis of elbasvir/grazoprevir phase 2 and 3 trials demonstrated an SVR12 rate of 100% (6/6) in genotype 1 patients with pretreatment NS5A RASs treated with elbasvir/grazoprevir for 16 or 18 weeks plus ribavirin ([Jacobson, 2015b](#)); ([Thompson, 2015](#)).

Based on known inferior response in patients with baseline NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for elbasvir/grazoprevir therapy. If baseline RASs are present (ie, substitutions at amino acid position 28, 30, 31, or 93), another recommended regimen should be selected.

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Related References

Afdhal NH, Zeuzem S, Kwo PY, et al. [Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection](#). *N Engl J Med*. 2014;370(20):1889-1898.

Brown RS, Hezode C, Wang S, et al. [Preliminary efficacy and safety of 8-week glecaprevir/pibrentasvir in patients with HCV genotype 1-6 infection and compensated cirrhosis: the EXPEDITION-8 study \[Abstract LB-7\]](#). *The Liver Meeting*. 2018.

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.

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.

Hezode C, Reau N, Svarovskaia ES, et al. [Resistance analysis in patients with genotype 1-6 HCV infection treated with sofosbuvir/velpatasvir in the phase III studies](#). *J Hepatol*. 2018;68(5):895-903.

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.

Jacobson IM, Lawitz E, Gane EJ, et al. [Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials](#). *Gastroenterology*. 2017;153(1):113-122.

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.

Lawitz EJ, Gane EJ, Pearlman B, et al. [Efficacy and safety of 12 wks vs 18 wks of treatment w/ GRZ and ELB w/ or without RBV for HCV GT1 infection in previously untreated pts w/ cirrhosis and pts w/ previous null response w/ or without cirrhosis \(C-WORTHY\), randomised, open-label phase 2 trial](#). *Lancet*. 2015;385(9973):1075-1086.

Mangia A, Milligan S, Khalili M, et al. [Global real-world evidence of sofosbuvir/velpatasvir as simple, effective HCV treatment: analysis of 5552 patients from 12 cohorts](#). *Liver Int*. 2020;40(8):1841-1852.

Rockstroh JK, Lacombe K, Viani RM, et al. [Efficacy and safety of glecaprevir/pibrentasvir in patients coinfecting with hepatitis C virus and human immunodeficiency virus type 1: the EXPEDITION-2 study](#). *Clin Infect Dis*. 2018;67(7):1010-1017. doi:10.1093/cid/ciy220.

Thompson A, Zeuzem S, Rockstroh JK, et al. [The combination of grazoprevir and elbasvir +RBV is highly effective for the treatment of GT1a-infected patients](#). *The Liver Meeting 2015*. 2015.

Zeuzem S, Ghalib R, Reddy KR, et al. [Grazoprevir-Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection: A Randomized Trial](#). *Ann Intern Med*. 2015;163(1):1-13.

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.
