


## Treatment-Naive Genotype 1a Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

### Treatment-Naive Genotype 1a Patients Without Cirrhosis

| RECOMMENDED  | DURATION | RATING  |
|--|----------|--|
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs for elbasvir <sup>a</sup>  | 12 weeks | I, A   |
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup>  | 8 weeks  | I, A   |
| Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)   | 12 weeks | I, A   |
| <hr/>  |          |  |
| Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are HIV-uninfected and whose HCV RNA level is <6 million IU/mL   | 8 weeks  | I, B   |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)   | 12 weeks | I, A   |
| <p><sup>a</sup> Includes genotype 1a resistance-associated substitutions (RASs) at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance. If 1 or more RASs are present, another recommended regimen should be used.</p> <p><sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.</p> |          |  |

## Recommended Regimens

### Elbasvir/Grazoprevir

The fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) is recommended based on data from the phase 3 C-EDGE trial, which assessed the efficacy and safety of this regimen for 12 weeks in treatment-naive adults (genotypes 1, 4, and 6) ([Zeuzem, 2015f](#)). Patients were enrolled from 60 centers in 9 countries on 4 continents. Three hundred eighty-two patients (91% of the study cohort) were infected with genotype 1 (50% genotype 1a, 41% genotype 1b). The sustained virologic response rates at 12 weeks (SVR12) were 92% (144/157) in treatment-naive patients with genotype 1a infection and 99% (129/131) in genotype 1b patients. Findings from this phase 3 study support earlier phase 2 findings from the C-WORTHY trial in which SVR12 rates of 92% (48/52) and 95% (21/22) were demonstrated among genotype 1a and genotype 1b treatment-naive, noncirrhotic patients, respectively, who received 12 weeks of elbasvir/grazoprevir without ribavirin ([Sulkowski, 2015b](#)). The C-WORTHY trial enrolled both HCV-monoinfected and HIV/HCV-coinfected patients.

The presence of certain baseline NS5A RASs significantly reduces SVR12 rates with a 12-week course of elbasvir/grazoprevir 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 an SVR12 rate of 99% (133/135) in patients without these RASs receiving 12 weeks of elbasvir/grazoprevir ([Zeuzem, 2017](#)). Among treatment-naive patients, the presence of baseline NS5A RASs with greater than 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.

In the phase 3 open-label C-EDGE TE trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, 58 genotype 1a-infected patients received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, and there were no virologic failures ([Kwo, 2017](#)). Subsequent integrated analysis of the 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 plus ribavirin for 16 or 18 weeks ([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 positions 28, 30, 31, or 93), another recommended regimen should be used (additional information is available in the [RAS](#) section).

## Glecaprevir/Pibrentasvir

The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) is administered as three 100 mg/40 mg fixed-dose combination pills. Based on favorable data for 8 weeks of treatment among noncirrhotic patients in the phase 2 SURVEYOR-1 study (33/34 patients with SVR and no virologic failures) ([Kwo, 2017b](#)), ENDURANCE-1 enrolled 703 noncirrhotic, genotype 1 patients who were DAA-naive or in whom a previous interferon-based regimen failed. Participants were randomized to receive 8 or 12 weeks of glecaprevir/pibrentasvir ([Zeuzem, 2016](#)). Of those enrolled, 43% had genotype 1a, 85% had fibrosis stage 0 or 1, and 62% were treatment naive. 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 to the 12-week arm. A single patient experienced on-treatment virologic failure in this study (genotype 1a, day 29). Notably, there were no documented relapses in either study arm.

EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir 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; SVR for genotype 1a was 98% (47/48) ([Forns, 2017](#)).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected adults with genotypes 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 was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection ([Rockstroh, 2017](#)). 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.

In an integrated analysis of 602 DAA-naive, noncirrhotic patients with genotype 1 infection treated with 8 weeks of glecaprevir/pibrentasvir in 6 phase 2 or 3 clinical trials, SVR12 was 99.2% (597/602) ([Naganuma, 2019](#)). Real-world cohorts from Germany (63% genotype 1a) and Italy (32% genotype 1a) show similarly high efficacy in treatment-naive, noncirrhotic patients with genotype 1 infection treated with 8 weeks of glecaprevir/pibrentasvir. Using a modified intention-to-treat analysis (excluding those not completing treatment or lost to follow-up), SVR was 100% in both the German (228/228) ([Berg, 2019](#)) and the Italian (307/307) ([D'Ambrosio, 2019](#)) cohorts.

## 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 was 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%).

ION-3 excluded patients with cirrhosis and investigated shortening therapy from 12 weeks to 8 weeks (with or without ribavirin) ([Kowdley, 2014](#)). SVR12 rates were 93% to 95% across all study arms with no difference in SVR in the intention-to-treat analysis. However, relapse rates were higher in the 8-week arms (20/431)—regardless of ribavirin use—compared with the 12-week arm (3/216). Post hoc analyses of the ribavirin-free arms assessed baseline predictors of relapse and identified lower relapse rates in patients who received 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels <6 million IU/mL (2%; 2/123). The same held true for patients with similar baseline HCV RNA levels who received 12 weeks of treatment (2%; 2/131). This analysis was not controlled, which limits the generalizability of this approach to clinical practice.

Published, real-world cohort data generally show comparable effectiveness of 8-week and 12-week courses of ledipasvir/sofosbuvir in treatment-naive patients without cirrhosis ([Backus, 2016](#)); ([Ingiliz, 2016](#)); ([Ioannou, 2016](#)); ([Kowdley, 2016](#)); ([Terrault, 2016](#)). However, only about half of patients eligible for 8 weeks of treatment received it, assignment of duration was not randomized, and baseline characteristics may have varied between 8- and 12-week groups.

Real-world cohort studies of ledipasvir/sofosbuvir for treatment-naive, noncirrhotic black patients reported lower SVR12 rates with shorter duration therapy compared to white patients, although the absolute difference in SVR12 rates was <5% ([Su, 2017](#)); ([Wilder, 2016](#)); ([O'Brien, 2014](#)); ([Ioannou, 2016](#)). A subsequent real-world study among a Northern California Kaiser Permanente cohort of 436 black patients—most of whom were treated with an 8-week regimen—found similar SVR12 rates with 8 and 12 weeks of therapy (95.6% and 95.8%, respectively) ([Marcus, 2018](#)). Similarly, a Maryland Veterans Health Administration real-world cohort of black patients with predominantly genotype 1 infection found SVR12 rates of 93.7% (131/140) and 91.4% (332/363) with 8- and 12-week regimens, respectively ([Tang, 2018](#)). These data coupled with the availability of excellent rescue therapies for patients in whom initial DAA therapy fails support the use of 8 weeks of ledipasvir/sofosbuvir for black patients without cirrhosis and HCV RNA <6 million IU/mL.

Based on available data, shortening treatment to less than 12 weeks is not recommended for HIV/HCV-coinfected patients (see [HIV/HCV Coinfection](#) section). For others with potential negative prognostic factors, shortening treatment duration should be done at the discretion of the practitioner.

## Sofosbuvir/Velpatasvir

The fixed-dose combination of 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) 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 SVR with no difference observed by subtype (98% 1a; 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (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 infection—with or without compensated 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 for 12 weeks, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR12 with a single relapse observed with each subtype.

In a single-arm, phase 3 study from Asia that included 375 treatment-naive and -experienced patients with genotype 1, 2, 3, 4, 5, or 6 infection (18% with cirrhosis) treated with 12 weeks of sofosbuvir/velpatasvir, SVR was achieved in 95% (362/375) ([Wei, 2019](#)). Of the 129 participants with genotype 1 infection (17% genotype 1a), 100% achieved SVR.

**Last update:** November 6, 2019

## 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.
- Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. [Real-world effectiveness and predictors of sustained virological response with all-oral therapy in 21,242 hepatitis C genotype-1 patients](#). *Antivir Ther*. 2017;22(6):481-493.
- Berg T, Naumann U, Stoehr A, et al. [Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of chronic hepatitis C infection: data from the German Hepatitis C-Registry](#). *Aliment Pharmacol Ther*. 2019;49(8):1052-1059. doi:10.1111/apt.15222.
- D'Ambrosio R, Pasulo L, Puoti M, et al. [Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C](#). *J Hepatol*. 2019;70(3):379-387. doi:10.1016/j.jhep.2018.11.011.
- 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.
- Ingiliz P, Christensen S, Kimhofer T, et al. [Sofosbuvir and ledipasvir for 8 weeks for the treatment of chronic hepatitis C virus \(HCV\) infection in HCV-monoinfected and HIV-HCV-coinfected individuals: results from the German hepatitis C cohort \(GECCO-01\)](#). *Clin Infect Dis*. 2016;63(10):1320-1324.
- Ioannou GN, Beste LA, Chang MF, et al. [Effectiveness of sofosbuvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir and dasabuvir regimens for treatment of patients with hepatitis C in the Veterans Affairs national health care system](#). *Gastroenterology*. 2016;151(3):457-471.e5.
- 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.
- Kowdley KV, Gordon SC, Reddy KR, et al. [Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis](#). *N Engl J Med*. 2014;370(20):1879-1888.
- Kowdley KV, Sundaram V, Jeon CY, et al. [Eight weeks of ledipasvir/sofosbuvir is effective for selected patients with genotype 1 hepatitis C virus infection](#). *Hepatology*. 2016;65(4):1094-1103.
- 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.
- Kwo PY, Poordad F, Asatryan A, et al. [Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis](#). *J Hepatol*. 2017;67(2):263-271.

- Marcus JL, Hurley LB, Chamberland S. [No difference in effectiveness of 8 vs 12 weeks of ledipasvir and sofosbuvir for treatment of hepatitis C in black patients](#). *Clin Gastroenterol Hepatol*. 2018;16(6):927-935. doi:10.1016/j.cgh.2018.03.003.
- Naganuma A, Chayama K, Notsumata K, et al. [Integrated analysis of 8-week glecaprevir/pibrentasvir in Japanese and overseas patients without cirrhosis and with hepatitis C virus genotype 1 or 2 infection](#). *J Gastroenterol*. 2019;54(8):752-761. doi:10.1007/s00535-019-01569-7.
- O'Brien TR, Lang Kuhs KA, Pfeiffer RM. [Subgroup differences in response to 8 weeks of ledipasvir/sofosbuvir for chronic hepatitis C](#). *Open Forum Infect Dis*. 2014;1(3):ofu110.
- Rockstroh J, Lacombe K, Viani RM, et al. [Efficacy and safety of Glecaprevir/Pibrentasvir in patients co-infected with hepatitis C virus and human immunodeficiency virus-1: the EXPEDITION-2 Study \[Abstract LBP-522\]](#). In: *The International Liver Congress. EASL. The International Liver Congress. EASL.*; 2017. Available at: [http://dx.doi.org/10.1016/S0168-8278\(17\)30467-1](http://dx.doi.org/10.1016/S0168-8278(17)30467-1).
- Su F, Green PK, Berry K, Ioannou GN. [The association between race/ethnicity and the effectiveness of direct antiviral agents for hepatitis C virus infection](#). *Hepatology*. 2016;65(2):426-438.
- Sulkowski MS, Hézode C, Gerstoft J, et al. [Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir \(MK-5172\) and elbasvir \(MK-8742\) with or without ribavirin in patients with HCV GT1 mono-infection and HIV/HCV coinfection \(C-WORTHY\): a randomised, open-label phase 2 trial](#). Vierling JM, Mallolas J, Pol S, et al., eds. *Lancet*. 2015;285(9973):1087-1097. doi:10.1016/S0140-6736(14)61793-1.
- Tang L, Parker A, Flores Y, et al. [Treatment of hepatitis C with 8 weeks of ledipasvir/sofosbuvir: highly effective in a predominantly black male patient population](#). *J Viral Hepat*. 2018;25(2):205-208. doi:10.1111/jvh.12796.
- Terrault NA, Zeuzem S, Di Bisceglie AM, et al. [HCV-TARGET study group. Effectiveness of ledipasvir-sofosbuvir combination in patients with hepatitis C virus infection and factors associated with sustained virologic response](#). *Gastroenterology*. 2016;151(6):1131-1140.e5.
- 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.
- Wei L, Lim SG, Xie Q, et al. [Sofosbuvir-velpatasvir for treatment of chronic hepatitis C virus infection in Asia: a single-arm, open-label, phase 3 trial](#). *Lancet Gastroenterol Hepatol*. 2019;4(2):127-134. doi:10.1016/S2468-1253(18)30343-1.
- Wilder JM, Jeffers LJ, Ravendhran N, et al. [Safety and efficacy of ledipasvir-sofosbuvir in black patients with hepatitis C virus infection: a retrospective analysis of phase 3 data](#). *Hepatology*. 2016;63(2):437-444.
- 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, Feld J, Wang S. [ENDURANCE-1: efficacy and safety of 8- versus 12-week treatment with ABT-493/ABT-530 in patients with chronic HCV genotype 1 infection \[abstract 253\]](#). In: *The Liver Meeting 2016*. The Liver Meeting 2016. Boston, MA; 2016.
- 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.