## Treatment-Naive Genotype 1a Without Cirrhosis

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

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

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<td>12 weeks</td>
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<tr>
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<td>8 weeks</td>
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<tr>
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<tr>
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<td>8 weeks</td>
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<table>
<thead>
<tr>
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<td>Daily simeprevir (150 mg) plus sofosbuvir (400 mg)</td>
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<tr>
<td>Daily daclatasvir (60 mg)(^c) plus sofosbuvir (400 mg)</td>
<td>12 weeks</td>
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<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RASs(^a) for elbasvir</td>
<td>16 weeks</td>
<td>IIa, B</td>
</tr>
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</table>

\(^a\) Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.

\(^b\) This is a 3-tablet coformulation. Please refer to the prescribing information.

\(^c\) 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.

For genotype 1a-infected, treatment-naive patients without cirrhosis, there are 4 recommended regimens with comparable efficacy. Four regimens are classified as alternative because, compared to the recommended regimens, they require a longer duration of treatment, involve greater prescribing complexity, are potentially less efficacious, and/or there are limited supporting data.
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.

Recommendations for prolonging treatment duration to 16 weeks with inclusion of ribavirin for treatment-naive genotype 1a patients with baseline NS5A RASs is 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-infected patients who received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, 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), treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥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 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 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, 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.

**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 a pair of 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 SVR 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 receiving 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels <6 million IU/mL (2/123; 2%). The same held true for patients with similar baseline HCV RNA levels who received 12 weeks of treatment (2/131; 2%). 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.

Based on available data, shortening treatment to less than 12 weeks is not recommended for HIV/HCV-coinfected patients (see HIV/HCV Coinfection section) and black patients (Su, 2016; Wilder, 2016; O’Brien, 2014; Ioannou, 2016). For others, it should be done at the discretion of the practitioner with consideration of other potential negative prognostic factors.

**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 SVR 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 genotypes 1, 2, 3, 4, 5, or 6—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, 170/172 (99%) with
genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed with each subtype.

**Alternative Regimens**

**Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir and Ribavirin**

The daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based ribavirin was approved by the FDA for the treatment of genotype 1a infection in treatment-naive patients based on 3 registration trials: SAPPHIRE-I (322 treatment-naive patients with genotype 1a infection without cirrhosis); PEARL-IV (305 treatment-naive patients with genotype 1a without cirrhosis); and TURQUOISE-II (261 treatment-naive and -experienced patients with genotype 1a and cirrhosis).

The SAPPHIRE-I trial reported a 95.3% SVR12 rate with 12 weeks of paritaprevir/ritonavir/ombitasvir + dasabuvir and ribavirin (Feld, 2014). Overall, virologic failure was higher for patients with genotype 1a (7/8 failures) than genotype 1b (1/8 failures). PEARL-IV was specifically designed to determine the role of paritaprevir/ritonavir/ombitasvir + dasabuvir—with or without weight-based ribavirin—for treatment-naive, genotype 1a-infected patients without cirrhosis (Ferenci, 2014).

SVR12 was lower in the ribavirin-free arm than in the ribavirin-containing arm (90% vs 97%, respectively) due to higher rates of virologic failure (7.8% vs 2%, respectively), confirming the need for weight-based ribavirin for patients with genotype 1a. An extended-release formulation of paritaprevir/ritonavir/ombitasvir + dasabuvir was approved in 2016, allowing once-daily dosing; ribavirin, when needed, remains at twice-daily dosing (AbbVie Inc, 2017).

**Simeprevir + Sofosbuvir**

The OPTIMIST-1 trial investigated the safety and efficacy of simeprevir (150 mg) and sofosbuvir (400 mg) in patients with genotype 1 without cirrhosis. In this study, 310 treatment-naive and -experienced patients without cirrhosis were randomly assigned to 12 or 8 weeks of the simeprevir plus sofosbuvir regimen (Kwo, 2016). Overall SVR12 rates were 97% (150/155) for the 12-week arm and 83% (128/155) for the 8-week arm, with a statistically significantly greater relapse rate in the 8-week arm. In the 12-week arm, there was no difference in SVR12 based on past treatment experience; treatment-naive and -experienced patients achieved SVR12 rates of 97% and 95%, respectively. There was also no difference in SVR12 based on genotype 1 subtype or the presence of the baseline Q80K resistance substitution.

**Daclatasvir + Sofosbuvir**

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for the treatment of genotype 1 infection is recommended based on data from the phase 3 ALLY-2 trial, which assessed the efficacy and safety of daclatasvir and sofosbuvir for 12 weeks in patients coinfected with HIV and HCV (genotype 1, 2, 3, or 4) (Wyles, 2015). One hundred twenty-three (83%) patients receiving 12 weeks of therapy in the trial were infected with genotype 1. Eighty-three (54%) of these patients were treatment naive. The SVR rate was 96% in treatment-naive patients with genotype 1a infection (n=71) receiving 12 weeks of therapy. Similarly, in a phase 2b study of daclatasvir plus sofosbuvir among 88 treatment-naive patients with genotype 1a infection—21 treated for 24 weeks (11 with ribavirin) and 67 treated for 12 weeks (33 with ribavirin)—there were no virologic relapses (Sulkowski, 2014a).

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