Initial Treatment of HCV Infection

Initial treatment of HCV infection includes patients with chronic hepatitis C who have not been previously treated with interferon, peginterferon, ribavirin, or any HCV direct-acting antiviral (DAA) agent, whether experimental, investigational, or US Food and Drug Administration (FDA) approved.

The level of evidence available to inform the best regimen for each patient and the strength of the recommendation vary, and are rated accordingly (see Methods Table 2). In addition, specific recommendations are given when treatment differs for a particular group (eg, those infected with different genotypes). Recommended regimens are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. In certain situations, an alternative regimen may be an optimal regimen for an individual patient. Not recommended regimens are clearly inferior compared to recommended or alternative regimens based on factors such as lower efficacy, unfavorable tolerability and toxicity, longer treatment duration, and/or higher pill burden. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection. Specific considerations for pediatric patients and persons with HIV/HCV coinfection, decompensated cirrhosis (moderate or severe hepatic impairment; Child-Turcotte-Pugh [CTP] class B or C), HCV infection post liver transplant, and severe renal impairment, end-stage renal disease (ESRD), or post kidney transplant are addressed in other sections of the guidance.

Simplification of the treatment regimen may expand the number of healthcare professionals who prescribe antiviral therapy and increase the number of persons treated. This would align with the National Academies of Science, Engineering, and Medicine strategy to reduce cases of chronic HCV infection by 90% by 2030 (NASEM, 2017).

Recommended and alternative regimens are listed in order of level of evidence. When several regimens are at the same recommendation level, they are listed in alphabetical order. Regimen choice should be determined based on patient-specific data, including drug-drug interactions. Patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response. All patients require careful monitoring during treatment, particularly for anemia if ribavirin is included in the regimen (see Monitoring section).

The following pages include guidance for management of treatment-naive patients.

- Genotype 1
- Genotype 2
- Genotype 3
- Genotype 4
- Genotype 5 or 6

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with DAAs are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration of treatment is unclear, expert consultation should be sought.

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Treatment-Naive Genotype 1

Four highly potent DAA combination regimens are recommended for patients with genotype 1 infection, although there are differences in the recommended regimens based on the HCV subtype, the presence or absence of baseline NS5A resistance-associated substitutions (RASs), and the presence or absence of compensated cirrhosis.

With certain regimens, patients with genotype 1a may have higher virologic failure rates than those with genotype 1b. Genotype 1 infection that cannot be subtyped should be treated as genotype 1a infection.

Approximately 10% to 15% of genotype 1-infected patients without prior exposure to NS5A inhibitors have detectable NS5A RASs prior to treatment. The clinical impact of NS5A RASs varies across regimens and baseline patient characteristics. In patients with genotype 1a infection, the presence of baseline NS5A RASs that cause a large reduction in the activity of NS5A inhibitors (>5 fold) adversely impacts response to some NS5A inhibitor-containing regimens (Zeuzem, 2017); (Jacobson, 2015b). These RASs are found by population sequencing in roughly 5% to 10% of patients and relevant RASs vary by DAA regimen. Given that baseline NS5A RASs are one of the strongest pretreatment predictors of therapeutic response with certain regimens in those with genotype 1a infection, testing for these RASs prior to deciding on a therapeutic course is recommended in select situations (Zeuzem, 2015c). For further guidance, please see the HCV Resistance Primer section.

Compared to interferon-based therapy, DAAs are associated with an increased risk of drug-drug interactions with concomitant medications. Thus, attention to drug interactions is an important treatment consideration (see Drug Interactions table). The product prescribing information and other resources (eg, http://www.hep-druginteractions.org ) should be referenced regularly to ensure safety when prescribing DAA regimens. Important interactions with commonly used medications (eg, antacids, lipid-lowering drugs, anti-epileptics, antiretrovirals, etc) exist for all the regimens discussed.

The following pages include guidance for management of treatment-naive patients with genotype 1 infection.

- Treatment-Naive Genotype 1a Without Cirrhosis
- Treatment-Naive Genotype 1b Without Cirrhosis
- Treatment-Naive Genotype 1a With Compensated Cirrhosis
- Treatment-Naive Genotype 1b With Compensated Cirrhosis

Last update: September 21, 2017
### Treatment-Naive Genotype 1a Without Cirrhosis

<table>
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<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
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<tbody>
<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs(^a) for elbasvir</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)(^b)</td>
<td>8 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
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<table>
<thead>
<tr>
<th>ALTERNATIVE</th>
<th>DURATION</th>
<th>RATING</th>
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</thead>
<tbody>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is &lt;6 million IU/mL</td>
<td>8 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
</tbody>
</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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### Treatment-Naive Genotype 1a With Compensated Cirrhosis

#### Recommended and alternative regimens listed by evidence level and alphabetically for:
#### Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
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<tbody>
<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs&lt;sup&gt;b&lt;/sup&gt; for elbasvir</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
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<table>
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<th>RATING</th>
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<tbody>
<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RASs&lt;sup&gt;b&lt;/sup&gt; for elbasvir</td>
<td>16 weeks</td>
<td>Iia, B</td>
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<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.

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

For genotype 1a-infected, treatment-naive patients with compensated cirrhosis, there are 4 recommended regimens with comparable efficacy. The alternative regimen is classified as such because, compared to the recommended regimens, it requires a longer duration of treatment, involves greater prescribing complexity, is potentially less efficacious, and/or there are limited supporting data.

### Recommended Regimens

**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 ([Lawitz, 2015c](#); [Zeuzem, 2017](#)).

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 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 duration of treatment 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 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 patients) 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 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

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; SVR 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, 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 2 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 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%).

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 SVR with no difference in SVR 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 genotype 1, 2, 3, 4, 5, or 6—19% with
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.

**Last update:** September 21, 2017
## Treatment-Naive Genotype 1b Without Cirrhosis

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

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

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<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)</td>
<td>8 weeks</td>
<td>I, A</td>
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<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
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- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL**

<table>
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<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>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)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily simeprevir (150 mg) plus sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily daclatasvir (60 mg)&lt;sup&gt;b&lt;/sup&gt; plus sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
</tbody>
</table>

- **Daily fixed-dose combination of simeprevir (150 mg) plus sofosbuvir (400 mg)**

### 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 SVR12 was 92% (144/157) in treatment-naive patients with genotype 1a and 99% (129/131) in those with genotype 1b. 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.

In contrast to genotype 1a, the presence of baseline substitutions associated with NS5A resistance did not appear to affect genotype 1b response to elbasvir/grazoprevir. Thus, current data do not support extending the treatment duration or adding ribavirin in genotype 1b patients with NS5A RASs.

**Glecaprevir/Pibrentasvir**

Based on favorable data for 8 weeks of treatment for 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 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, 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 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. All genotype 1b patients achieved SVR (Forns, 2017).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected persons 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 rates were 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 ledipasvir/sofosbuvir 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 and 12 weeks 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 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-infected 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 either 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 in each subtype.

**Alternative Regimens**

**Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir**

The daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) was approved by the FDA for the treatment of genotype 1b infection in treatment-naive patients based on 3 registration trials; 2 focused specifically on those without cirrhosis. SAPPHIRE-I, which included 151 treatment-naive, genotype 1b-infected patients without cirrhosis, reported an SVR12 rate of 98% with 12 weeks of paritaprevir/ritonavir/ombitasvir + dasabuvir in these patients (Feld, 2014).

Given the high SVR12 rates seen in SAPPHIRE-I, PEARL-III was specifically designed to determine the role of weight-based ribavirin with paritaprevir/ritonavir/ombitasvir + dasabuvir in treatment-naive, genotype 1b-infected patients without cirrhosis, reported an SVR12 rate of 98% with 12 weeks of paritaprevir/ritonavir/ombitasvir + dasabuvir in these patients (Feld, 2014).

GARNET, a phase 3b single-arm study of 163 genotype 1b patients without cirrhosis, demonstrated a 98% SVR rate with an 8-week course of paritaprevir/ritonavir/ombitasvir + dasabuvir. When considering the generalizability of these results, it is important to note that 91% of the GARNET participants had fibrosis stage 0 to 2, 93% had HCV RNA levels <6 million IU/mL, and 96% were white. In addition, 2 of the 15 patients with fibrosis stage 3 experienced virologic relapse, suggesting that if used, an 8-week strategy should be reserved for those with early-stage fibrosis (Welzel, 2016b).
Simeprevir + Sofosbuvir

The OPTIMIST-1 trial investigated the safety and efficacy of simeprevir (150 mg) plus 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 weeks or 8 weeks of the simeprevir plus sofosbuvir regimen (Kwo, 2016). Overall SVR12 rates were 97% (150/155) in the 12-week arm and 83% (128/155) in 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/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. Only 12 had genotype 1b and all achieved SVR12 (Wyles, 2015). Furthermore, in the ALLY-1 study, all 11 genotype 1b-infected patients with advanced cirrhosis achieved SVR12. Due to the limited numbers of genotype 1b patients represented in the phase 3 trials of this regimen, there is not enough evidence to support a different approach by subtype at this time.

Last update: September 21, 2017
Treatment-Naive Genotype 1b With Compensated Cirrhosis

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

<table>
<thead>
<tr>
<th>Treatment-Naive Genotype 1b Patients With Compensated Cirrhosisa</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RECOMMENDED</strong></td>
<td><strong>DURATION</strong></td>
</tr>
<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)b</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
</tr>
<tr>
<td><strong>ALTERNATIVE</strong></td>
<td><strong>DURATION</strong></td>
</tr>
<tr>
<td>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)c</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

a For decompensated cirrhosis, please refer to the appropriate section.
b This is a 3-tablet coformulation. Please refer to the prescribing information.
c Please see statement on FDA warning regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

For genotype 1b-infected, treatment-naive patients with compensated cirrhosis, there are 4 recommended regimens with comparable efficacy. The alternative regimen is classified as such because, compared to the recommended regimens, it requires a longer duration of treatment, involves greater prescribing complexity, is potentially less efficacious, and/or there are limited supporting data.

**Recommended Regimens**

**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 the 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 (Lawitz, 2015c); (Zeuzem, 2017).

**Glecaprevir/Pibrentasvir**

EXPEDITION-1 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 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; all genotype
1b patients achieved SVR (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 daily 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 2 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 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%).

**Sofosbuvir/Velpatasvir**

The daily fixed-dose combination of 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 SVR with no difference in SVR observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 98% achieved SVR (99%). 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—19% with compensated cirrhosis—to receive either 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 Regimen**

**Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir**

The daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) was approved by the FDA for the treatment of genotype 1b infection in treatment-naive patients based on 3 registration trials: SAPPHIRE-I (151 treatment-naive patients with genotype 1b without cirrhosis); PEARL-III (419 treatment-naive patients with genotype 1b without cirrhosis); and TURQUOISE-II (119 treatment-naive and -experienced patients with genotype 1b and cirrhosis). TURQUOISE-II enrolled treatment-naive and -experienced patients with Child-Turcotte-Pugh class A cirrhosis to receive either 12 weeks or 24 weeks of paritaprevir/ritonavir/ombitasvir + dasabuvir and ribavirin. Overall SVR12 rates were 98.5% in the 12-week arm and 100% in the 24-week arm (Poordad, 2014).

To address the need for ribavirin with this regimen in patients with genotype 1b and cirrhosis, the TURQUOISE-III study evaluated the safety and efficacy of paritaprevir/ritonavir/ombitasvir + dasabuvir without ribavirin for 12 weeks in patients with genotype 1b infection and compensated cirrhosis. Sixty patients (62% men; 55% treatment-experienced; 83% with the IL28B non-CC genotype; 22% with platelet counts <90 x 10^5/L; 17% with albumin <3.5 g/dL) were enrolled. All patients
completed treatment and all achieved SVR12. Based on this study, treating patients with genotype 1b with paritaprevir/ritonavir/ombitasvir + dasabuvir without ribavirin is recommended, regardless of prior treatment experience or the presence of compensated cirrhosis (Feld, 2016).

**Last update:** September 21, 2017
Treatment-Naive Genotype 2

The following pages include guidance for management of treatment-naive patients with genotype 2 infection.

- Treatment-Naive Genotype 2 Without Cirrhosis
- Treatment-Naive Genotype 2 With Compensated Cirrhosis

Last update: September 21, 2017
Treatment-Naive Genotype 2 Without Cirrhosis

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

Treatment-Naive Genotype 2 Patients Without Cirrhosis

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)(^a)</td>
<td>8 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALTERNATIVE</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily daclatasvir (60 mg)(^b) plus sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>Ila, B</td>
</tr>
</tbody>
</table>

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

\(^b\) 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

Glecaprevir/Pibrentasvir

ENDURANCE-2 was a randomized, double-blind, placebo-controlled trial 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 among 302 genotype 2-infected treatment-naive or -experienced participants. Treatment-experienced patients included those previously treated with interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon. Patients randomized to placebo later received open-label treatment with glecaprevir/pibrentasvir for 12 weeks. Among 202 patients randomized to active treatment, 70% (141/202) were treatment naive and none had cirrhosis. The SVR12 rates were 99% and 100% by intention-to-treat and modified intention-to-treat analysis, respectively. There were no virologic failures. One participant who achieved SVR4 was lost to follow-up before the SVR12 evaluation. There was no effect of baseline RASs on SVR12 rate. Overall, therapy was well tolerated and the adverse event profile was not different compared to placebo (Asselah, 2018b).

A shorter duration of glecaprevir/pibrentasvir for 8 weeks was evaluated in the SURVEYOR-II, part 4 study. This was a single-arm, phase 2 study that evaluated glecaprevir/pibrentasvir for 8 weeks among 203 treatment-naive or -experienced patients (previously treated with interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 2, 4, 5, or 6 infection without cirrhosis. Of the 142 genotype 2-infected patients, 137 (96%) were treatment naive. Among the treatment-naive, genotype 2-infected participants, 135/137 (99%) achieved SVR12. The presence of baseline RASs had minimal effect on SVR12 rates. Fifty-three of 126 (42%) treatment-naive and -experienced participants with genotype 2 had the L31M RAS within the NS5A gene at baseline. Fifty-one of 53 (96%) of these participants achieved SVR12 (Asselah, 2018b).

While not a head-to-head comparison, the results of ENDURANCE-2 and SURVEYOR-II, part 4 indicate that glecaprevir/pibrentasvir administered for 8 or 12 weeks is highly efficacious among genotype 2-infected, treatment-naive patients without cirrhosis.
Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 2 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-2 compared 12 weeks of sofosbuvir/velpatasvir to 12 weeks of sofosbuvir plus ribavirin in 266 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis. The study showed superior efficacy of sofosbuvir/velpatasvir (SVR12 99% vs 94%); (Foster, 2015a). ASTRAL-1 also included 104 genotype 2 treatment-naive and -experienced participants without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (Feld, 2015). Pooled analysis of all genotype 2 patients in ASTRAL-1 and ASTRAL-2 demonstrated 100% SVR12 in participants with compensated cirrhosis (29/29) and 99% SVR12 in treatment-naive participants (194/195). Among patients with genotype 2 receiving sofosbuvir/velpatasvir, the presence of baseline NS5A or NS5B RASs was not associated with virologic failure (Asselah, 2018).

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) versus 12 weeks of sofosbuvir/velpatasvir. Fifty-three patients with genotype 2 were included in the sofosbuvir/velpatasvir arm and all achieved SVR12 (100%). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2 infection (Jacobson, 2017).

Alternative Regimen

Daclatasvir + Sofosbuvir

A 12-week course of daclatasvir (60 mg) plus sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. Although this regimen was not approved for the treatment of genotype 2 infection, daclatasvir maintains adequate activity against genotype 2 despite a 50% effective concentration (EC_{50}) that increases by several logs in the presence of the prevalent M31 substitution (Wang, 2014). In fact, daclatasvir plus sofosbuvir was associated with high SVR rates in treatment-naive patients with genotype 2 infection with both 12 weeks and 24 weeks of therapy (Wyles, 2015); (Sulkowski, 2014a). It is unclear if there is a subgroup of genotype 2-infected patients who would benefit from extending treatment. For patients who require treatment but cannot tolerate sofosbuvir/velpatasvir or glecaprevir/pibrentasvir, a regimen of daclatasvir plus sofosbuvir for 12 weeks is reasonable.

Last update: September 21, 2017
### Treatment-Naive Genotype 2 With Compensated Cirrhosis

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

#### Treatment-Naive Genotype 2 Patients With Compensated Cirrhosis

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12 weeks</td>
<td>I, B</td>
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</table>

**ALTERNATIVE**

<table>
<thead>
<tr>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily daclatasvir (60 mg)&lt;sup&gt;c&lt;/sup&gt; plus sofosbuvir (400 mg)</td>
<td>16 to 24 weeks</td>
</tr>
</tbody>
</table>

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<sup>a</sup> For **decompensated cirrhosis**, please refer to the appropriate section.<br>
<sup>b</sup> This is a 3-tablet coformulation. Please refer to the prescribing information.<br>
<sup>c</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.

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### Recommended Regimens

**Sofosbuvir/Velpatasvir**

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 2 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-2 compared 12 weeks of sofosbuvir/velpatasvir to 12 weeks of sofosbuvir plus ribavirin in 266 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis. The study showed superior efficacy of sofosbuvir/velpatasvir compared to sofosbuvir plus ribavirin (SVR12 99% vs 94%); (<cite>Foster, 2015a</cite>). ASTRAL-1 also included 104 genotype 2 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (<cite>Feld, 2015</cite>). Pooled analysis of all genotype 2 patients in ASTRAL-1 and ASTRAL-2 demonstrated 100% SVR12 in those with compensated cirrhosis (29/29) and 99% SVR12 in treatment-naive participants (194/195). Among patients with genotype 2 receiving sofosbuvir/velpatasvir, the presence of baseline NS5A or NS5B RASs was not associated with virologic failure (<cite>Asselah, 2018</cite>).

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) versus 12 weeks of sofosbuvir/velpatasvir. Fifty-three patients with genotype 2 were included in the sofosbuvir/velpatasvir arm and all achieved SVR12 (100%). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2 infection (<cite>Jacobson, 2017</cite>).

**Glecaprevir/Pibrentasvir**

EXPEDITION-1 was a multicenter, open-label, single-arm, phase 3 trial that enrolled 146 treatment-naive or -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. Participants were treated with 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. Across all
genotypes, 145/146 (99%) achieved SVR12 (Forns, 2017). EXPEDITION-1 included 31 treatment-naive and -experienced persons with genotype 2 infection and compensated cirrhosis; all achieved SVR12. Baseline NS5A RASs were detected (by next-generation sequencing using a 15% detection cutoff) in 40% of 133 tested participants. Baseline NS5A RASs had no effect on SVR rates among treatment-naive and -experienced patients with genotype 2 infection.

**Alternative Regimen**

**Daclatasvir + Sofosbuvir**

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. Although this regimen was not approved for the treatment of genotype 2 infection, daclatasvir maintains adequate activity against genotype 2 despite a 50% effective concentration ($EC_{50}$) that increases by several logs in the presence of the prevalent M31 substitution (Wang, 2014). In fact, daclatasvir with sofosbuvir was associated with high SVR rates in treatment-naive patients with genotype 2 infection with both 12 weeks and 24 weeks of therapy (Wyles, 2015); (Sulkowski, 2014a). It is unclear if there is a subgroup of genotype 2-infected patients who would benefit from extending treatment. For patients who require treatment but cannot tolerate sofosbuvir/velpatasvir or glecaprevir/pibrentasvir, a regimen of daclatasvir with sofosbuvir for 12 weeks is reasonable.

Last update: September 21, 2017
Treatment-Naive Genotype 3

The following pages include guidance for management of treatment-naive patients with genotype 3 infection.

- Treatment-Naive Genotype 3 Without Cirrhosis
- Treatment-Naive Genotype 3 With Compensated Cirrhosis

Last update: September 21, 2017
Treatment-Naive Genotype 3 Without Cirrhosis

Recommended and alternative regimens listed alphabetically for:

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
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<tbody>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) (^a)</td>
<td>8 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
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<table>
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<tr>
<th>ALTERNATIVE</th>
<th>DURATION</th>
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<tbody>
<tr>
<td>Daily daclatasvir (60 mg) (^b) plus sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
</tbody>
</table>

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

\(^b\) 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

Glecaprevir/Pibrentasvir

ENDURANCE-3 was a randomized (2:1) trial comparing 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, to 12 weeks of sofosbuvir (400 mg) and daclatasvir (60 mg) among 348 treatment-naive participants with genotype 3 infection without cirrhosis. The trial was later amended to include an open-label arm that evaluated glecaprevir/pibrentasvir for an 8-week duration among 157 treatment-naive participants with genotype 3 infection without cirrhosis. Participants receiving glecaprevir/pibrentasvir for 8 or 12 weeks achieved an SVR12 rate of 95% in an intention-to-treat analysis (222/233 participants receiving the 12-week regimen; 149/157 participants receiving the 8-week regimen) (Foster, 2017). Virologic failure was observed in 6 participants receiving the 8-week regimen (1 virologic breakthrough; 5 relapses) and in 4 participants in the 12-week arm (1 virologic breakthrough; 3 relapses). Both the 8- and 12-week glecaprevir/pibrentasvir regimens met noninferiority criteria for SVR12 compared to the standard of care arm of sofosbuvir/daclatasvir, which reported an SVR12 rate of 97%. While the baseline presence of the Y93H substitution did not affect SVR rates (10/10 with Y93H achieved SVR with an 8 week duration vs 165/171 without Y93H), the presence of the A30K substitution was associated with a lower SVR rate (14/18 with A30K achieved SVR with an 8 week duration vs 161/163 without A30K) (Krishnan, 2018). Of the 14 treatment-naive patients with genotype 3 without cirrhosis with baseline A30K who received a 12 week duration of glecaprevir/pibrentasvir, 13/14 achieved SVR. Given the small numbers, there is insufficient evidence to recommend testing for RASs or extension of therapy in the setting of A30K at this time, but the effect of the A30K mutation should continue to be explored in real world cohorts. These data support an 8-week regimen of glecaprevir/pibrentasvir for the treatment of genotype 3-infected patients who are treatment-naive without cirrhosis.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-3 demonstrated superiority of 12 weeks of sofosbuvir/velpatasvir to 24 weeks sofosbuvir plus ribavirin in 552 treatment-naive and
Treatment-Naive
From www.HCVGuidance.org on September 03, 2019

Among treatment-naive, noncirrhotic patients, SVR12 rates were 98% (160/163) for sofosbuvir/velpatasvir compared to 90% (141/156) for sofosbuvir plus ribavirin. Among patients with compensated cirrhosis, SVR12 was 93% (40/43) for sofosbuvir/velpatasvir compared to 73% (33/45) for sofosbuvir plus ribavirin. Of the 250 participants who received sofosbuvir/velpatasvir, 43 (16%) had baseline NS5A RASs, of which 88% achieved SVR12 compared to 97% without baseline RASs. Eighty-four percent (21/25) with Y93H achieved SVR12. Pending further data on optimal therapy in the setting of a baseline Y93 substitution, the addition of ribavirin is recommended for patients with cirrhosis.

The phase 3 POLARIS-2 study evaluated 12 weeks of sofosbuvir/velpatasvir in genotype 3-infected, noncirrhotic patients who were either treatment-naive or interferon-experienced. Eighty-nine genotype 3 patients received the sofosbuvir/velpatasvir regimen and 97% achieved SVR12 (86/89) (Jacobson, 2017). There were no virologic failures. This confirms the efficacy of sofosbuvir/velpatasvir in genotype 3-infected patients without cirrhosis.

### Alternative Regimen

**Daclatasvir + Sofosbuvir**

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection. The recommendation is based on ALLY-3, a phase 3 study of the once-daily NS5A inhibitor daclatasvir plus sofosbuvir for 12 weeks among genotype 3-infected, treatment-naive or -experienced (interferon ± ribavirin, sofosbuvir plus ribavirin, or other anti-HCV agents) patients. The study included 101 treatment-naive patients and demonstrated an SVR12 rate of 90%. Among treatment-naive patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12; in treatment-naive patients with compensated cirrhosis (Metavir F4), 58% achieved SVR12 (Nelson, 2015). This suggests that patients with genotype 3 infection and compensated cirrhosis are likely to benefit from an extension of therapy.

Baseline NS5A RASs significantly reduce SVR12 rates with a 12-week course of daclatasvir/sofosbuvir in genotype 3-infected patients. In an analysis of 175 genotype 3-infected patients with nucleotide sequence data from the ALLY-3 trial, the presence of a NS5A Y93H was associated with a reduced SVR12 rate; 54% (7/13) in those with the substitution compared to 92% (149/162) in those without it (Nelson, 2015). Although the small numbers make interpretation difficult, only 7% of participants (13/175) had NS5A Y93H, all of which were subtype 3a. SVR rates were numerically lower among those with both cirrhosis and Y93H. In noncirrhotic patients with Y93H, 67% (6/9) achieved SVR12 compared to 98% (125/128) among noncirrhotics without Y93H. In those with both cirrhosis and Y93H, 25% (1/4) achieved SVR12 compared to 71% (24/34) in those with cirrhosis but without the Y93H substitution (Daklinza PI).

Substitutions A30K, L31F, L31I in the genotype 3a replicon are associated with reduced daclatasvir susceptibility (Daklinza PI). In the ALLY-3 trial, participants with A30K and without cirrhosis achieved 100% SVR12 (9/9); those with compensated cirrhosis had lower SVR12 rates (1/5); (Nelson, 2015). The impact of this single substitution is difficult to discern as 2/5 patients had compound substitutions with Y93H. Pending further data on optimal therapy, the addition of ribavirin for patients with cirrhosis is recommended in the setting of a baseline Y93 substitution.

ENDURANCE-3 was a randomized (2:1) trial comparing 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, to 12 weeks of daclatasvir/sofosbuvir among 348 treatment-naive participants with genotype 3 infection without cirrhosis. In the 115 patients randomized to daclatasvir/sofosbuvir, 97% achieved SVR12, and 20 of 21 participants (95%) with baseline NS5A RAS achieved SVR (Foster, 2017).

**Last update:** September 21, 2017
Treatment-Naive Genotype 3 With Compensated Cirrhosis

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

| Treatment-Naive Genotype 3 Patients With Compensated Cirrhosis<sup>a</sup> |
|--------------------------|-----------------|------------------|
| **RECOMMENDED**          | **DURATION**    | **RATING**       |
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)<sup>b</sup> | 12 weeks | I, A |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)<sup>c</sup> | 12 weeks | I, A |

| **ALTERNATIVE**          | **DURATION**    | **RATING**       |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) when Y93H is present | 12 weeks | IIa, B |
| Daily daclatasvir (60 mg)<sup>d</sup> plus sofosbuvir (400 mg) with or without weight-based ribavirin<sup>c</sup> | 24 weeks | IIa, B |

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

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

<sup>c</sup> RAS testing for Y93H is recommended for cirrhotic patients. If present, ribavirin should be included in the regimen or sofosbuvir/velpatasvir/voxilaprevir should be considered.

<sup>d</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

**Glecaprevir/Pibrentasvir**

SURVEYOR-II—a partially randomized, open-label, multicenter, 4-part, phase 2 trial—compared 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, to glecaprevir/pibrentasvir plus ribavirin among 48 treatment-naive, genotype 3-infected participants with compensated cirrhosis. All patients treated with 12 weeks of glecaprevir/pibrentasvir, with or without ribavirin, achieved SVR12 ([Kwo, 2016b](#)). The presence of baseline NS3 and/or NS5A RASs had no impact on SVR12 rate regardless of inclusion of ribavirin in the treatment regimen; however the analysis was limited because few patients had NS5A RASs. These data indicate that 12 weeks of glecaprevir/pibrentasvir yields high SVR12 rates among treatment-naive, genotype 3-infected patients with compensated cirrhosis.

**Sofosbuvir/Velpatasvir**

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-3 randomized 552 treatment-naive and -experienced patients (without cirrhosis or with compensated cirrhosis) to 12 weeks of sofosbuvir/velpatasvir or 24 weeks sofosbuvir plus ribavirin ([Foster, 2015a](#)). Among those with compensated cirrhosis, the
SVR12 was 93% (40/43) in the sofosbuvir/velpatasvir arm compared to 73% (33/45) among those in the sofosbuvir plus ribavirin arm. Of the 250 participants who received sofosbuvir/velpatasvir, 43 (16%) had baseline NS5A RASs, of which 88% achieved SVR12 compared to 97% without baseline substitutions. Eighty-four percent (21/25) of those with Y93H achieved SVR12. Pending further data on optimal therapy in the setting of a baseline Y93 substitution, the addition of ribavirin is recommended for patients with compensated cirrhosis.

POLARIS-3 was a randomized, phase 3 trial that compared 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) to 12 weeks of sofosbuvir/velpatasvir among 219 DAA-naive participants with genotype 3 infection and cirrhosis (Jacobson, 2017). The SVR12 rate was 96% in both arms; 105/109 of those randomized to 12 weeks of sofosbuvir/velpatasvir achieved SVR. Four participants in the sofosbuvir/velpatasvir arm had the Y93H substitution; all achieved SVR12.

### Alternative Regimens

#### Sofosbuvir/Velpatasvir/Voxilaprevir

POLARIS-3 was a randomized, phase 3 trial that compared 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) to 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) among 219 DAA-naive participants with genotype 3 infection and cirrhosis (Jacobson, 2017). Thirty-one percent of participants were interferon treatment experienced. The SVR12 rate was 96% in both arms, 106/110 of patients randomized to 8 weeks of sofosbuvir/velpatasvir/voxilaprevir and 105/109 of those randomized to 12 weeks of sofosbuvir/velpatasvir. There were 2 virologic failures in each arm (2 relapses in the sofosbuvir/velpatasvir/voxilaprevir arm; 1 virologic breakthrough and 1 relapse in the sofosbuvir/velpatasvir arm). Baseline RASs had no effect on treatment response. Among the 6 participants with Y93H in the sofosbuvir/velpatasvir/voxilaprevir arm and 4 in the sofosbuvir/velpatasvir arm, all achieved SVR12. Additionally, no patients receiving sofosbuvir/velpatasvir/voxilaprevir with virologic failure developed RASs. Although an 8-week regimen was studied in POLARIS-3, a 12-week regimen of sofosbuvir/velpatasvir/voxilaprevir was approved by the FDA for the indication of retreatment of DAA-experienced patients and could be considered as an alternative regimen for patients with cirrhosis and Y93H.

#### Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks was approved by the FDA for treatment of genotype 3 infection. The recommendation is based on ALLY-3, a phase 3 study of daclatasvir/sofosbuvir for 12 weeks among genotype 3-infected, treatment-naive or -experienced (interferon ± ribavirin, sofosbuvir plus ribavirin, or other anti-HCV agents) patients. The study included 101 treatment-naive patients and demonstrated an SVR12 rate of 90%. In treatment-naive patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12, compared to 58% SVR12 in treatment-naive patients with cirrhosis (Metavir F4) (Nelson, 2015).

The results of the ALLY-3 study suggest that patients with genotype 3 infection and cirrhosis are likely to benefit from an extension of therapy. This has been confirmed in cohort studies, including the European compassionate-use program, which reported SVR12 rates of 70% vs 86% when daclatasvir/sofosbuvir was used for 12 weeks and 24 weeks in genotype 3-infected patients with cirrhosis, respectively. The role of ribavirin could not be clarified as only 4 patients received daclatasvir/sofosbuvir plus ribavirin for 12 weeks, all of which achieved SVR12. SVR12 was comparable between the 24-week arms irrespective of the addition of ribavirin (85.9% [116/135] without ribavirin; 81.3% [39/48] with ribavirin). SVR12 rates were also higher in those with compensated Child-Pugh A cirrhosis (85% to 90%) compared to 70.6% in Child-Pugh B/C. Again, the addition of ribavirin did not increase SVR12 rates in the 24-week treatment arms (Hézode, 2017). Seventy-three percent of patients were treatment-experienced, however earlier data suggested that SVR12 rates were higher in treatment-naive patients (91% to 100%) compared to treatment-experienced (81% to 82%). SVR12 rates were similar in patients who received ribavirin (88%, 29/33) and those who did not (86%, 42/49) (Hézode, 2017).

Baseline NS5A RASs significantly reduce SVR12 rates with a 12-week course of daclatasvir/sofosbuvir in genotype...
3-infected patients. In an analysis of 175 genotype 3-infected patients with nucleotide sequence data from the ALLY-3 trial, the presence of a NS5A Y93H was associated with a reduced SVR12 rate; 54% (7/13) in those with the substitution compared to 92% in those without it (149/162). Although the small numbers make interpretation difficult, only 7% of participants (13/175) had NS5A Y93H, all of which were subtype 3a. SVR rates were numerically lower among those with both cirrhosis and Y93H. In noncirrhotic patients with Y93H, 67% (6/9) achieved SVR12 compared to 98% (125/128) among noncirrhotics without Y93H. In those with both cirrhosis and Y93H, 25% (1/4) achieved SVR12 compared to 71% (24/34) in those with cirrhosis but without the Y93H substitution (Daklinza PI, 2016).

Substitutions A30K, L31F, L31I in the genotype 3a replicon are associated with reduced daclatasvir susceptibility (Daklinza PI, 2016). In the ALLY-3 trial, participants with A30K and without cirrhosis achieved 100% SVR12 (9/9); those with cirrhosis had lower SVR12 rates (1/5) (Nelson, 2015). The impact of this single substitution is difficult to discern as 2/5 patients had compound substitutions with Y93H. Pending further data on optimal therapy, the addition of ribavirin for patients with cirrhosis is recommended in the setting of a baseline Y93 substitution.

**Last update:** September 21, 2017
Treatment-Naive Genotype 4

The following pages include guidance for management of treatment-naive patients with genotype 4 infection.

- Treatment-Naive Genotype 4 Without Cirrhosis
- Treatment-Naive Genotype 4 With Compensated Cirrhosis

Last update: September 21, 2017
Treatment-Naive Genotype 4 Without Cirrhosis

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

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<td>RECOMMENDED</td>
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<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
</tr>
<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
</tr>
<tr>
<td>ALTERNATIVE</td>
</tr>
<tr>
<td>Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin</td>
</tr>
</tbody>
</table>

*a This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Glecaprevir/Pibrentasvir

Based on favorable data for 12 weeks of treatment for noncirrhotic patients in part 4 of the phase 2 SURVEYOR-2 study (100% SVR12 in 34 patients with genotype 4, 5, or 6) (Kwo, 2017b), ENDURANCE-4 enrolled 121 DAA-naive or -experienced (sofosbuvir plus ribavirin ± peginterferon) genotype 4, 5, or 6 patients without cirrhosis to receive 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 (Asselah, 2018b). Of those enrolled, 86% had fibrosis stage F0 to F1 and 68% were treatment naive. The genotype distribution was 63% genotype 4, 21% genotype 5, and 16% genotype 6. The overall SVR12 rate for the intention-to-treat population was 99% (120/121), including 99% (75/76) for genotype 4, 100% for genotype 5 (26/26), and 100% (19/19) for genotype 6. (Asselah, 2018b). Based on these studies, glecaprevir/pibrentasvir was approved for treatment of genotype 4-infected, DAA-naive, noncirrhotic patients for a duration of 8 weeks.

Genotype 4, 5, and 6 patients were not included in the randomized study to compare an 8-week versus 12-week course of glecaprevir/pibrentasvir for DAA-naive, noncirrhotic patients. However, part 4 of the SURVEYOR-2 study investigated an 8-week course of glecaprevir/pibrentasvir in DAA-naive patients without cirrhosis (Asselah, 2018b). In the intention-to-treat analysis, 43/46 with genotype 4, 2/2 with genotype 5, and 9/10 with genotype 6 achieved SVR 12; there were no known virologic failures.

EXPEDITION-1 investigated use of glecaprevir/pibrentasvir in treatment-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, 99% (145/146) achieved SVR12, including 16/16 (100%) with genotype 4, 2/2 (100%) with genotype 5, and 7/7 (100%) with genotype 6 (Forns, 2017). Based on these studies, glecaprevir/pibrentasvir was approved for treatment of genotype 4-infected, DAA-naive, noncirrhotic patients for a duration of 8 weeks.
Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 4 infection in patients with or without cirrhosis. ASTRAL-1 included 64 genotype 4-infected, treatment-naive patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (100%) (Feld, 2015).

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) versus 12 weeks of sofosbuvir/velpatasvir. Of 57 patients with genotype 4 in the sofosbuvir/velpatasvir arm, 98% achieved SVR and 1 patient experienced relapse (Jacobson, 2017).

Elbasvir/Grazoprevir

A phase 2/3 trial evaluated 66 treatment-naive, genotype 4 patients treated with daily elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks. Ten patients had weight-based ribavirin added to the regimen and 56 did not. Six participants (9.1%) were cirrhotic and 28 (42.4%) had HIV/HCV coinfection. Overall, 97% (64/66) achieved SVR12. There was 1 treatment failure and 1 patient was lost to follow-up. The impact of ribavirin could not be assessed, however the addition of ribavirin numerically increased the SVR12 rate in treatment-experienced participants. Baseline RASs and genotype subtype did not appear to impact SVR12 rates (Asselah, 2018c).

Ledipasvir/Sofosbuvir

The SYNERGY trial was an open-label study evaluating 12 weeks of ledipasvir (90 mg)/sofosbuvir (400 mg) in 21 genotype 4-infected patients, of whom 60% were treatment naive and 43% had advanced fibrosis (Metavir stage F3 or F4) (Kohli, 2015). One patient took the first dose and then withdrew consent. The 20 patients who completed treatment all achieved SVR12; thus, the SVR12 rate was 95% in the intention-to-treat analysis and 100% in the per-protocol analysis. Abergel and colleagues reported data from an open-label, single-arm study including 22 genotype 4-infected, treatment-naive patients (1 with cirrhosis) with an SVR12 rate of 95% (21/22) (Abergel, 2016). These pilot studies support the use of ledipasvir/sofosbuvir in patients with genotype 4 infection.

Alternative Regimen

Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

PEARL-I was a randomized, open-label, phase 2b study that included a cohort of 86 treatment-naive patients with genotype 4 infection without cirrhosis who received 12 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg), with or without weight-based ribavirin. SVR12 rates were 100% (42/42) in the ribavirin arm and 90.9% (40/44) in the group not receiving ribavirin. Adverse effects were generally mild, with headache, asthenia, fatigue, and nausea most commonly reported. There were no discontinuations owing to adverse events (Hézode, 2015).

The AGATE-I trial randomized 120 treatment-naive and -experienced patients with genotype 4 infection and compensated cirrhosis to receive 12 weeks or 16 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated (Asselah, 2015a). Similarly, the AGATE-II trial offered 100 treatment-naive and -experienced (interferon-based regimens) noncirrhotic patients with genotype 4 infection paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin for 12 weeks. The SVR12 was 94%. These data support the use of a 12-week course of paritaprevir/ritonavir/ombitasvir plus ribavirin in treatment-experienced genotype 4 patients (Esmat, 2015).

Last update: September 21, 2017
## Treatment-Naive Genotype 4 With Compensated Cirrhosis

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

### Treatment-Naive Genotype 4 Patients With Compensated Cirrhosis\(^a\)

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
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<tbody>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)(^b)</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)</td>
<td>12 weeks</td>
<td>IIa, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>IIa, B</td>
</tr>
</tbody>
</table>

### ALTERNATIVE                                                                 | DURATION | RATING |
| Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin\(^c\) | 12 weeks | I, A   |

\(^a\) For [decompensated cirrhosis](#), please refer to the appropriate section.

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

\(^c\) Please see statement on FDA [warning](#) regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

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### Recommended Regimens

**Sofosbuvir/Velpatasvir**

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 4 infection in patients with or without cirrhosis. ASTRAL-1 included 64 genotype 4-infected, treatment-naive patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (100%) ([Feld, 2015](#)).

The POLARIS-2 phase 3 study randomized DAA-naive patients (19% with compensated cirrhosis, overall) to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) or 12 weeks of sofosbuvir/velpatasvir. Of 57 patients with genotype 4 in the sofosbuvir/velpatasvir arm, 98% achieved SVR and 1 patient experienced relapse ([Jacobson, 2017](#)).

**Glecaprevir/Pibrentasvir**

EXPEDITION-1 was a multicenter, open-label, single-arm, phase 3 trial that enrolled 146 treatment-naive or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. Patients received 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. Across all genotypes, 145/146 (99%) achieved SVR12 ([Forns, 2017](#)). EXPEDITION-1 included 16 treatment-naive and -experienced genotype 4-infected participants with compensated cirrhosis. All 16 patients achieved SVR12. Baseline...
NS5A RASs were detected by next-generation sequencing (using a 15% detection cutoff) in 40% of 133 tested participants. Baseline NS5A RASs had no effect on SVR rates among treatment-naive and -experienced participants with genotype 4. Based on this study, a 12-week course of glecaprevir/pibrentasvir is recommended for genotype 4-infected, treatment-naive patients with compensated cirrhosis.

**Elbasvir/Grazoprevir**

A phase 2/3 trial evaluated 66 treatment-naive, genotype 4 patients treated with daily elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks. Ten patients had weight-based ribavirin added to the regimen and 56 did not. Six participants (9.1%) were cirrhotic and 28 (42.4%) had HIV/HCV coinfection. Overall, 97% (64/66) achieved SVR12. There was 1 treatment failure and 1 patient was lost to follow-up. The impact of ribavirin could not be assessed, however the addition of ribavirin numerically increased the SVR12 rate in treatment-experienced participants. Baseline RASs and subtype did not appear to impact SVR12 rates (Asselah, 2018c).

**Ledipasvir/Sofosbuvir**

The SYNERGY trial was an open-label study evaluating 12 weeks of ledipasvir (90 mg)/sofosbuvir (400 mg) in 21 genotype 4-infected patients, of whom 60% were treatment naive and 43% had advanced fibrosis (Metavir stage F3 or F4) (Kohli, 2015). One patient took the first dose and then withdrew consent. The 20 patients who completed treatment all achieved SVR12; thus, the SVR12 rate was 95% in the intention-to-treat analysis and 100% in the per-protocol analysis. Abergel and colleagues reported data from an open-label, single-arm study including 22 genotype 4-infected, treatment-naive patients (1 with cirrhosis) with an SVR12 rate of 95% (21/22) (Abergel, 2016). These pilot studies support the use of ledipasvir/sofosbuvir in patients with genotype 4 infection.

**Alternative Regimen**

**Paritaprevir/Ritonavir/Ombitasvir + Ribavirin**

PEARL-I was a randomized, open-label phase 2b study that included a cohort of 86 treatment-naive patients with genotype 4 infection without cirrhosis who received 12 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg), with or without weight-based ribavirin. SVR12 rates were 100% (42/42) in the ribavirin arm and 90.9% (40/44) in the group not receiving ribavirin. Adverse effects were generally mild, with headache, asthenia, fatigue, and nausea most commonly reported. There were no discontinuations owing to adverse events (Hézode, 2015).

The AGATE-I trial randomized 120 treatment-naive and -experienced patients with genotype 4 infection and compensated cirrhosis to receive 12 weeks or 16 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated (Asselah, 2015a). Similarly, the AGATE-II trial offered 100 treatment-naive and -experienced (interferon-based regimens) noncirrhotic patients with genotype 4 infection paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin for 12 weeks. The SVR12 was 94%. Additionally, AGATE-II randomized 60 treatment-naive and -experienced genotype 4-infected patients with compensated cirrhosis to receive either 12 or 24 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR rate from the 12-week arm was 97%. These data support the use of a 12-week course of paritaprevir/ritonavir/ombitasvir plus ribavirin in treatment-experienced genotype 4 patients, including those with cirrhosis (Esmat, 2015).

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### Recommended Regimens

#### Glecaprevir/Pibrentasvir

Based on favorable data for 12 weeks of treatment for noncirrhotic patients in the phase 2 SURVEYOR-2 study (100% SVR12 in 34 patients with genotype 4, 5, or 6) ([Kwo, 2017b](#)), ENDURANCE-4 enrolled 121 DAA-naive or -experienced (sofosbuvir plus ribavirin ± peginterferon) genotype 4, 5, or 6 patients without cirrhosis to receive 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg pills ([Asselah, 2018b](#)). Of those enrolled, 86% had fibrosis stage F0 to F1 and 68% were treatment naive. The genotype distribution was 63% genotype 4, 21% genotype 5, and 16% genotype 6. The overall SVR12 rate for the intention-to-treat population was 99% (120/121), including 99% (75/76) for genotype 4, 100% for genotype 5 (26/26), and 100% (19/19) for genotype 6.

Genotype 4, 5, and 6 patients were not included in the randomized study to compare an 8-week vs 12-week course for DAA-naive, noncirrhotic patients. However, part 4 of the SURVEYOR-2 study investigated an 8-week course of glecaprevir/pibrentasvir in DAA-naive patients without cirrhosis ([Asselah, 2018b](#)). In the intention-to-treat analysis, 2/2 with genotype 5 and 9/10 with genotype 6 achieved SVR 12; there were no known virologic failures.

In addition, 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, 99% (145/146) achieved SVR12, including 2/2 with genotype 5 and 7/7 with genotype 6 ([Forns, 2017](#)). Based on these studies, glecaprevir/pibrentasvir was approved for an 8-week course (noncirrhotic) and 12-week course (cirrhotic) of treatment for people with genotype 5.

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### Recommended Regimens listed by evidence level and alphabetically for:

#### Treatment-Naive Genotype 5 or 6 Patients With and Without Compensated Cirrhosis

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)(^b)</td>
<td>8 weeks (no cirrhosis)</td>
<td>I, A</td>
</tr>
<tr>
<td></td>
<td>12 weeks (cirrhosis)</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>IIa, B</td>
</tr>
</tbody>
</table>

\(^a\) For decompensated cirrhosis, please refer to the appropriate section.

\(^b\) This is a 3-tablet coformulation. Please refer to the prescribing information.
or genotype 6 infection.

**Sofosbuvir/Velpatasvir**

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 5 and 6 infection in patients with and without cirrhosis (Feld, 2015). ASTRAL-1 included 24 genotype 5 treatment-naive participants with and without cirrhosis, 23 (96%) of whom achieved SVR12. The study also included 38 genotype 6 treatment-naive participants with and without cirrhosis, all of whom achieved SVR12 (100%). An additional 9 genotype 6 patients received sofosbuvir/velpatasvir in the POLARIS-2 phase 3 study, all of whom achieved SVR (Jacobson, 2017).

**Ledipasvir/Sofosbuvir**

Although there are limited data on patients with genotype 5 infection, the in vitro activity of sofosbuvir and ledipasvir are quite good with EC$_{50}$ of 15 nM and 0.081 nM, respectively. Abergel and colleagues reported data from an open-label, single-arm study that included 41 genotype 5-infected patients with an overall SVR12 rate of 95% (39/41) (Abergel, 2016). The SVR12 rate was also 95% specifically in treatment-naive patients (20/21), of whom only 3 had cirrhosis but all achieved SVR12.

Ledipasvir has in vitro activity against most genotype 6 subtypes, except for 6e (Wong, 2013; Kohler, 2014). A small, 2-center, open-label study (NCT01826981) investigated the safety and in vivo efficacy of ledipasvir/sofosbuvir for 12 weeks in treatment-naive and -experienced patients with genotype 6 infection. Twenty-five patients (92% were treatment-naive) who were primarily Asian (88%) had infection from 7 different subtypes (32% 6a; 24% 6e; 12% 6i; 8% 6m; 12% 6p; 8% 6q; 4% 6r). Two patients (8%) had cirrhosis. The SVR12 rate was 96% (24/25), and the single patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events (Gane, 2015).

**Last update:** September 21, 2017
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