

## Patients With Decompensated Cirrhosis

### Recommended for All Patients With HCV Infection Who Have Decompensated Cirrhosis <sup>i</sup>

RECOMMENDED	RATING <sup>i</sup>
Patients with HCV infection who have decompensated cirrhosis—moderate or severe hepatic impairment, ie, Child-Turcotte-Pugh (CTP) class B or class C—should be referred to a medical practitioner with expertise in that condition, ideally in a liver transplant center.	I, C


Clinical trial data demonstrate that in the population of persons with decompensated cirrhosis, most patients receiving direct-acting antiviral (DAA) therapy experience improvement in clinical and biochemical indicators of liver disease between baseline and post-treatment week 12, including patients with CTP class C cirrhosis ([Manns, 2016](#)); ([Curry, 2015](#)); ([Charlton, 2015](#)); ([Welzel, 2016](#)). However, improvements may be insufficient to avoid liver-related death or the need for liver transplantation ([Belli, 2016](#)), highlighting that not everyone benefits from DAA therapy ([Fernandez-Carrillo, 2016](#)). Most deaths among those receiving DAA therapy relate to the severity of underlying liver disease. The predictors of improvement or decline have not been clearly identified, though patients with a Model for End-Stage Liver Disease (MELD) score >20 or severe portal hypertension complications may be less likely to improve and might be better served by transplantation than treatment ([Terrault, 2017](#)); ([Belli, 2016](#)).

Real-world data comparing DAA response rates demonstrate that patients with cirrhosis and hepatocellular carcinoma (HCC) have lower SVR rates than cirrhotics without HCC ([Prenner, 2017](#)); ([Beste, 2017](#)). In a large VA study including sofosbuvir, ledipasvir/sofosbuvir, and paritaprevir/ritonavir/ombitasvir plus dasabuvir regimens (with and without ribavirin), overall SVR rates were 91% in patients without HCC vs 74% in those with HCC ([Beste, 2017](#)). After adjusting for confounders, the presence of HCC was associated with a lower likelihood of SVR (AOR=0.38). Whether this lower rate of SVR can be overcome with an extended duration of therapy is unknown.

## Decompensated Cirrhosis Genotype 1, 4, 5, or 6 Infection

Recommended regimens listed by evidence level and alphabetically for:

### Patients With Decompensated Cirrhosis<sup>a</sup> Who Have Genotype 1, 4, 5, or 6 Infection and Are Ribavirin Eligible

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, A <sup>b</sup>
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin <sup>c</sup>	12 weeks	I, A <sup>d</sup>
<b>Genotype 1 or 4 infection only:</b> Daily daclatasvir (60 mg) <sup>e</sup> plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, B

<sup>a</sup> Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.

<sup>b</sup> Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.


<sup>c</sup> Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.

<sup>d</sup> Only available data for genotype 6 are in patients with compensated cirrhosis.

<sup>e</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 for daclatasvir.

Recommended regimens listed by evidence level and alphabetically for:

### Patients With Decompensated Cirrhosis<sup>a</sup> Who Have Genotype 1, 4, 5, or 6 Infection and Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	24 weeks	I, A <sup>b</sup>
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	24 weeks	I, A <sup>c</sup>
<b>Genotype 1 or 4 infection only:</b> Daily daclatasvir (60 mg) <sup>d</sup> plus sofosbuvir (400 mg)	24 weeks	II, C

<sup>a</sup> Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.


<sup>b</sup> Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.

<sup>c</sup> Only available data for genotype 6 are in patients with compensated cirrhosis.

<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 for daclatasvir.

Recommended regimens listed by evidence level and alphabetically for:

## Patients With Decompensated Cirrhosis<sup>a</sup> and Genotype 1, 4, 5, or 6 Infection in Whom Prior Sofosbuvir- or NS5A-Based Treatment Failed

RECOMMENDED	DURATION	RATING 
<b>Prior sofosbuvir-based treatment failure only:</b> Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg; increase as tolerated)	24 weeks	II, C <sup>b</sup>
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin <sup>c</sup>	24 weeks	II, C <sup>d</sup>

<sup>a</sup> Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.

<sup>b</sup> Only available data for genotype 6 are in patients with compensated cirrhosis.

<sup>c</sup> Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis.

<sup>d</sup> Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.

### Ledipasvir/Sofosbuvir

The US-based, multicenter, randomized, open-label, phase 2 SOLAR-1 trial included 108 patients with genotype 1 or 4 infection and decompensated cirrhosis; 59 were categorized as CTP class B (score 7 to 9) and 49 were categorized as CTP class C (score 10 to 12). Participants were randomly assigned to 12 weeks or 24 weeks of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin (initial dose of 600 mg, increased as tolerated) ([Charlton, 2015b](#)). After excluding the 7 patients who underwent liver transplantation during the study, the SVR rate was 87% in CTP class B patients who received 12 weeks of treatment and 89% in those who received 24 weeks of treatment. Similarly, the SVR rates were 86% and 87%, respectively, with 12 weeks and 24 weeks of antiviral therapy in the CTP class C patients. Post-therapy virologic relapse occurred in 8% and 5% of the 12- and 24-week groups, respectively.

In the majority of participants with CTP class B or C disease, the MELD and CTP scores decreased between baseline and post-treatment week 4. As expected, the frequency of serious adverse events increased with treatment duration in both the CTP class B group (10% week 12; 34% week 24) and the CTP class C group (26% week 12; 42% week 24). Most of the serious adverse events were related to ribavirin. The mean daily dose of ribavirin in the patients with decompensated cirrhosis was 600 mg. Therapy was discontinued in 7% of the CTP class B patients and 8% of the CTP class C patients in the 24-week treatment arm.

The multicenter (Europe, Canada, Australia, and New Zealand), randomized, open-label, phase 2 SOLAR-2 study included 160 genotype 1- or 4-infected patients with decompensated cirrhosis (CTP class B or C). Study participants, who were treatment-naïve or -experienced, were randomly assigned to 12 weeks or 24 weeks of daily fixed-dose ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin (initial dose of 600 mg, increased as tolerated). All participants had a hemoglobin level >10 g/dL and an estimated glomerular filtration rate (eGFR) >40 mL/min ([Manns, 2016](#)). Among the 150 patients with decompensated cirrhosis who completed therapy and had evaluable efficacy results, SVR12 was achieved in 85% (61/72) of those in the 12-week study arm (90% [43/48] CTP class B; 75% [18/24] CTP class C). SVR 12 was achieved by 90% (70/78) of patients with decompensated cirrhosis in the 24-week study (98% [47/48] CTP class B ; 77% [23/30] CTP class C). Post-therapy virologic relapse occurred in 6% (9/150) of the patients with decompensated cirrhosis who completed therapy (7 in 12-week arm; 2 in 24-week arm).

Baseline CTP and MELD scores improved in the majority of the treated patients, but some participants experienced

worsening hepatic function. Among nontransplanted patients whose MELD score was  $\geq 15$  at baseline, 80% (20/25) had a MELD score  $< 15$  at SVR12. Among those with a MELD score  $< 15$  at baseline, 4% (2/56) had a MELD score  $\geq 15$  at SVR12. During the study, 8% (13/160) of the enrolled patients with decompensated cirrhosis (2 CTP class B, 11 CTP class C) died from various causes but none of the deaths were attributed to antiviral therapy. Serious adverse events occurred in approximately 28% of patients with decompensated cirrhosis with no significant difference between the 12-week and 24-week treatment arms.

A multicenter, double-blind study from France reported on the use of daily ledipasvir/sofosbuvir for 24 weeks compared to daily ledipasvir/sofosbuvir plus ribavirin for 12 weeks (with a 12-week placebo phase). Study participants included 154 patients with compensated cirrhosis and genotype 1 infection in whom prior peginterferon/ribavirin treatment failed (for most patients, treatment with peginterferon/ribavirin plus a protease inhibitor also failed) ([Bourliere, 2015](#)). The mean MELD score was 7 (range, 6 to 16), 26% of patients had varices, and 13% had low serum albumin levels. The SVR12 rate was 96% with the 12-week regimen and 97% with the 24-week regimen. The most common adverse events were asthenia, headache, and pruritus; the frequency of severe adverse events and the need for early drug discontinuation were low in both treatment groups. In light of these results, it is reasonable to consider daily ledipasvir/sofosbuvir plus ribavirin for 12 weeks in patients with decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed.

Collectively, these results indicate that a 12-week course of ledipasvir/sofosbuvir and ribavirin (initial dose of 600 mg, increased as tolerated) is an appropriate regimen for patients with decompensated cirrhosis and genotype 1 or 4 infection. Such therapy may lead to objective improvements in hepatic function and reduce the likelihood of recurrent HCV infection after subsequent transplantation. Most patients received a ribavirin dose of 600 mg/d. Of 17 patients (16 genotype 1; 1 genotype 4) in the SOLAR-1 and SOLAR-2 trials (6 CPT class B; 11 CPT class C) who received ledipasvir/sofosbuvir plus ribavirin for 12 weeks or 24 weeks prior to or up to the time of liver transplant, all had HCV RNA  $< 15$  IU/mL at the time of transplantation. Sixteen of the 17 patients achieved post-transplant SVR12; 1 patient died at post-op day 15, but the HCV RNA was  $< 15$  IU/mL on day 14 ([Yoshida, 2017](#)).

Real-world cohort studies have reported SVR rates in patients with decompensated cirrhosis. Foster and colleagues reported on the use of ledipasvir (90 mg)/sofosbuvir (400 mg) or daclatasvir (60 mg)/sofosbuvir (400 mg), with or without ribavirin, for 12 weeks in 235 genotype 1-infected patients from the United Kingdom ([Foster, 2016](#)). The SVR rates were similar in the 235 genotype participants receiving ledipasvir/sofosbuvir plus ribavirin or ledipasvir/sofosbuvir (86% and 81%, respectively). In this observational cohort study, 91% of the patients received ribavirin; only 6% discontinued ribavirin while 20% required a ribavirin dose reduction. MELD scores improved in 42% of treated patients and worsened in 11%. There were 14 deaths and 26% of the patients had a serious adverse event; none were treatment related.

The multicenter, prospective, observational HCV-TARGET study examined the real-world efficacy of ledipasvir/sofosbuvir (with or without ribavirin) for various treatment durations. The SVR12 rate among genotype 1 patients with a history of clinically decompensated cirrhosis was 90% (263/293) among evaluable patients ([Terrault, 2016](#)). In this cohort, 29% of patients with decompensated cirrhosis were treated with ribavirin and 48% received 24 weeks treatment.

A phase 2a, open-label study of 14 patients with compensated cirrhosis and genotype 1 infection in whom prior sofosbuvir-based therapy failed demonstrated that ledipasvir/sofosbuvir for 12 weeks was associated with a 100% SVR rate ([Osinusi, 2014](#)). In addition, results of an open-label, phase 2 study of 51 genotype 1-infected patients in whom prior sofosbuvir-based therapy failed demonstrated that a 12-week course of ledipasvir/sofosbuvir plus weight-based ribavirin (1000 mg/d to 1200 mg/d) led to an overall SVR12 rate of 98%, including 100% (14/14) among those patients with compensated cirrhosis ([Wyles, 2015b](#)).

## Sofosbuvir/Velpatasvir

The phase 3, open-label, multicenter, randomized ASTRAL-4 study enrolled 267 patients with genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B at the time of screening) who were treatment naive (45%) or experienced (55%). Notably, 10% of patients were CTP class A or class C at treatment baseline. Patients were randomly assigned (1:1:1 ratio) to 12 weeks of a daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg); 12 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin (1000 mg/d, weight  $< 75$  kg; 1200 mg/d, weight  $\geq 75$  kg); or 24 weeks of sofosbuvir/velpatasvir. Randomization was stratified by HCV genotype. All participants had a hemoglobin level  $> 10$  g/dL

and an eGFR  $\geq 50$  mL/min ([Curry, 2015b](#)). The genotype/subtype distribution of the participants was 60% (159/267) genotype 1a; 18% (48/267) genotype 1b; 4% (12/267) genotype 2; 15% (39/267) genotype 3; 3% (8/267) genotype 4; and <1% (1/267) genotype 6. Ninety-five percent of patients had a baseline MELD score  $\leq 15$ .

The SVR rates were 83% among those in the 12-week sofosbuvir/velpatasvir study arm, 94% in the 12-week sofosbuvir/velpatasvir plus ribavirin arm, and 86% in the 24-week sofosbuvir/velpatasvir arm. Among patients with genotype 1 infection, the SVR rates were 88%, 96%, and 92%, respectively. Twenty-two participants had virologic failure, including 20 patients with relapse and 2 patients (genotype 3) with on-treatment virologic breakthrough. The presence of baseline NS5A resistant substitutions was not associated with virologic relapse.

At post-treatment week 12, 47% of patients had an improvement in CTP score, 42% had no change, and 11% had an increased CTP score. Nine patients (3%) died due to various causes during the study; no deaths were judged to be related to antiviral therapy. Serious adverse events were reported in 16% to 19% of the treated patients. Anemia (ie, hemoglobin <10 g/dL) was reported in 23% of the group receiving ribavirin, and 8% and 9% in those who received 12 weeks and 24 weeks of sofosbuvir/velpatasvir without ribavirin, respectively.

A phase 2, open-label, single-arm study conducted by Gane and colleagues evaluated a 24-week course of sofosbuvir/velpatasvir plus weight-based ribavirin among 65 patients with a history of treatment failure with an NS5A-containing regimen ([Gane, 2016](#)). Twenty-six percent of enrolled patients had compensated cirrhosis. The overall SVR12 rate was 91% (59/65), including 97% (33/34) among genotype 1-infected patients, 91% (13/14) in those with genotype 2 infection, and 76% (13/17) in patients with genotype 3. To date, there are no data for this regimen given for 24 weeks in patients with decompensated cirrhosis.

The phase 3, multicenter ASTRAL-1 trial evaluated the efficacy and safety of a 12-week course of daily fixed-dose sofosbuvir/velpatasvir among treatment-naive and -experienced patients with genotype 1, 2, 4, 5, or 6 infection. The study included 35 patients with genotype 5 infection and 41 patients with genotype 6 infection ([Feld, 2015](#)). The overall SVR12 rates were 97% (34/35) in genotype 5-infected patients and 100% (41/41) in those with genotype 6 infection. Of note, 100% SVR12 was achieved in the small number of genotype 5 patients (n=5) and genotype 6 patients (n=6) with compensated cirrhosis enrolled in ASTRAL-1.

## Daclatasvir + Sofosbuvir

The phase 3, open-label ALLY-1 trial evaluated the efficacy and safety of 12 weeks of daily daclatasvir (60 mg) and sofosbuvir (400 mg) plus ribavirin (600 mg with possible escalation to 1000 mg as tolerated) among patients with cirrhosis (CTP class A, B, or C; n=60) or HCV recurrence after liver transplantation (n=53). Treatment-naive and -experienced patients were enrolled. More than 75% of participants had genotype 1 infection, although patients with genotype 2, 3, or 4 infection were also represented in the cirrhosis cohort. The CTP breakdown was 20% (12/60) class A, 53% (32/60) class B, and 26% (16/60) class C.

The SVR12 rates were 83% (50/60) among those in the cirrhosis group and 94% (50/53) among those with recurrent HCV infection post liver transplant. In the population with cirrhosis, SVR12 rates by genotype were: 82% (37/45) genotype 1; 80% (4/5) genotype 2; 83% (5/6) genotype 3; and 100% (4/4) genotype 4. Response rates differed based on severity of cirrhosis; SVR12 rates were 92% (11/12) among those with CTP class A cirrhosis, 94% (30/32) among those with class B, and 56% (9/16) in patients with class C cirrhosis ([Poordad, 2016](#)).

An observational cohort study from the United Kingdom conducted by Foster and colleagues examined various combinations of DAA agents in patients with decompensated cirrhosis (CTP score  $\geq 7$ ), recurrent HCV after liver transplantation, or a severe extrahepatic manifestation of HCV disease. The study treatment regimens included a 12-week course of daclatasvir plus sofosbuvir, with or without ribavirin. Among the 200 genotype 1-infected patients with decompensated cirrhosis enrolled in the study, the SVR12 for 12 weeks of daclatasvir/sofosbuvir plus ribavirin was 88% (30/34). SVR12 for daclatasvir/sofosbuvir without ribavirin was 50%, but only 4 patients received this regimen ([Foster, 2016](#)).

Overall SVR12 rates were similar in the genotype 1-infected participants receiving ledipasvir/sofosbuvir plus ribavirin or



ledipasvir/sofosbuvir (86% and 81%, respectively) and those receiving daclatasvir/sofosbuvir with ribavirin or daclatasvir/sofosbuvir therapy (82% and 60%, respectively). In this real-world study, 91% of the patients received ribavirin; only 6% discontinued ribavirin but 20% required a ribavirin dose reduction. MELD scores improved in 42% of treated patients and worsened in 11%. There were 14 deaths and 26% of the participants had a serious adverse event; none were treatment related. These data highlight the lower efficacy and increased safety concerns when treating patients with more advanced liver failure.

## Protease-Inhibitor Containing Regimens

To date, the fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) has not been rigorously studied in patients with decompensated cirrhosis. A phase 2, nonrandomized, open-label study of elbasvir/grazoprevir for 12 weeks was completed in 30 genotype 1-infected patients with CTP class B cirrhosis ([Jacobson, 2015](#)). The SVR12 rate was 90% (27/30); 1 patient died of liver failure at post-treatment week 4 and 2 patients relapsed. MELD scores improved in 15 treated patients, were unchanged in 9, and increased in 6. However, there are no safety or efficacy data regarding the US Food and Drug Administration (FDA)-approved elbasvir/grazoprevir doses in patients with decompensated cirrhosis. Therefore, until further data are available, treatment of patients with decompensated cirrhosis with elbasvir/grazoprevir is not recommended.

Recent data reported by the FDA have demonstrated that some patients with compensated cirrhosis treated with paritaprevir/ritonavir/ombitasvir  $\pm$  dasabuvir may develop rapid-onset direct hyperbilirubinemia without ALT elevation within 1 to 4 weeks of starting treatment, which can lead to rapidly progressive liver failure and death. A multicenter cohort study from Israel reported 7 patients who received paritaprevir/ritonavir/ombitasvir plus dasabuvir developed decompensation within 1 to 8 weeks of starting therapy, including 1 patient who died ([Zuckerman, 2016](#)). Therefore, paritaprevir/ritonavir/ombitasvir  $\pm$  dasabuvir is contraindicated in all patients with decompensated cirrhosis due to concerns about hepatotoxicity. In addition, all patients with compensated cirrhosis receiving this regimen should be monitored for clinical signs and symptoms of hepatic decompensation and undergo hepatic laboratory testing at baseline and at least every 4 weeks while on therapy.


The daily fixed dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills has not been studied in patients with decompensated cirrhosis and, pending additional safety data, is not recommended.

Similarly, the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) has not been studied in patients with hepatic decompensation. Thus, this regimen is not recommended for patients with decompensated cirrhosis (CTP class B or C) until further data are available.

## Decompensated Cirrhosis Genotype 2 or 3 Infection

Recommended Regimens listed by evidence level and alphabetically for:

### Patients With Decompensated Cirrhosis<sup>a</sup> Who Have Genotype 2 or 3 Infection and Are Ribavirin Eligible


RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin	12 weeks	I, A
Daily daclatasvir (60 mg) <sup>b</sup> plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, B

<sup>a</sup> Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.

<sup>b</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 for daclatasvir.

Recommended regimens listed by evidence level and alphabetically for:

### Patients With Decompensated Cirrhosis<sup>a</sup> Who Have Genotype 2 or 3 Infection and Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	24 weeks	I, A
Daily daclatasvir (60 mg) <sup>b</sup> plus sofosbuvir (400 mg)	24 weeks	II, C

<sup>a</sup> Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.

<sup>b</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 for daclatasvir.

Recommended regimens listed by evidence level and alphabetically for:

## Patients With Decompensated Cirrhosis<sup>a</sup> and Genotype 2 or 3 Infection in Whom Prior Sofosbuvir- or NS5A-Based Treatment Failed

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin <sup>b</sup>	24 weeks	II, C

<sup>a</sup> Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.

<sup>b</sup> Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.

### Sofosbuvir/Velpatasvir

The phase 3, open-label, multicenter, randomized ASTRAL-4 study enrolled 267 patients with genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B at the time of screening) who were treatment naive (45%) or experienced (55%). Patients were randomly assigned (1:1:1 ratio) to 12 weeks of a daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg); 12 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin (1000 mg/d, weight <75 kg; 1200 mg/d, weight ≥75 kg); or 24 weeks of sofosbuvir/velpatasvir. Randomization was stratified by HCV genotype.

The SVR rates among the 12 patients with CTP class B cirrhosis and genotype 2 infection were 100% (8/8) with sofosbuvir/velpatasvir for 12 weeks (with or without ribavirin), and 75% (3/4) with sofosbuvir/velpatasvir for 24 weeks. Among 39 patients with CTP class B cirrhosis with genotype 3 infection, the SVR rates were 50% (7/14) for 12 weeks of sofosbuvir/velpatasvir without ribavirin, 85% (11/13) for 12 weeks of sofosbuvir/velpatasvir plus ribavirin, and 50% (6/12) for 24 weeks of sofosbuvir/velpatasvir. Therefore, genotype 3-infected patients in particular appear to benefit from the addition of ribavirin to the regimen ([Curry, 2015b](#)). For patients with decompensated cirrhosis who are ribavirin ineligible, sofosbuvir/velpatasvir for 24 weeks is currently recommended, but additional studies involving larger numbers of patients are needed to define the optimal duration of therapy.

Sofosbuvir/velpatasvir has not been studied in CTP class C patients. There are no data on the outcomes of patients with decompensated cirrhosis and a history of prior sofosbuvir plus NS5A failure. However, among 69 patients (28% with compensated cirrhosis) with prior NS5A failure treated with sofosbuvir/velpatasvir plus ribavirin for 24 weeks, the SVR rates were 97% for genotype 1 (83% with compensated cirrhosis), 93% (13/14) for genotype 2 (no patients with cirrhosis), and 78% (75% with compensated cirrhosis) for genotype 3 ([Gane, 2017](#)).

### Daclatasvir + Sofosbuvir

Daily 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 and with cirrhosis. Although daclatasvir/sofosbuvir was not approved for the treatment of genotype 2 infection, daclatasvir maintains adequate activity against genotype 2 despite a 50% effective concentration (EC<sub>50</sub>) that increases by several logs in the presence of the prevalent M31 substitution ([Wang, 2014](#)). In clinical trials, daclatasvir/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, 2014](#)). It is unclear if there is a subgroup of genotype 2-infected patients who would benefit from extending treatment to 24 weeks. For patients with genotype 2 infection who require treatment but cannot tolerate ribavirin, an alternative regimen of daclatasvir/sofosbuvir for 12 weeks is



recommended with consideration of extending treatment to 24 weeks for patients with poor baseline characteristics (ie, decompensated cirrhosis).

Relevant data from the ALLY-1 study support use of daclatasvir/sofosbuvir plus ribavirin in patients with genotype 2 or 3 infection who have decompensated cirrhosis. Sixty patients with predominantly (80%) decompensated cirrhosis (CPT class B/C) were treated with daclatasvir/sofosbuvir plus ribavirin (600 mg/d, increased to tolerability). SVR rates were 80% (4/5) for genotype 2 patients and 83% (5/6) for genotype 3 patients with advanced cirrhosis ([Poordad, 2016](#)).

Broader experiences with treatment of genotype 3-infected patients with decompensated cirrhosis have been reported from real-world cohort studies. In a cohort from the United Kingdom, 110 patients with decompensated cirrhosis and genotype 3 infection treated with daclatasvir/sofosbuvir with or without ribavirin (600 mg/d, increased to tolerability) demonstrated SVR12 rates of 71% (75/105) and 60% (3/5), respectively ([Foster, 2016](#)). In comparison, among 62 patients with decompensated cirrhosis and genotype 3 infection treated with ledipasvir/sofosbuvir with or without ribavirin, the SVR12 rates were 65% (37/57) and 40% (2/5), respectively. In a multicenter Spanish study of daclatasvir/sofosbuvir with or without ribavirin in 123 genotype 3-infected patients (71% receiving 24 weeks), SVR12 was 94% in both CPT class A and CPT class B/C patients ([Alonso, 2017](#)). However, compared to CPT class A patients, the CPT class B/C patients had more frequent serious adverse events (16.7% vs 3.6%) and episodes of hepatic decompensation (5.2% vs 2.3%).

### Protease-Inhibitor Containing Regimens

The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills has activity against genotypes 2 and 3 but has not been studied in patients with decompensated cirrhosis. Pending additional safety data, this regimen is not recommended.

Similarly, the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) is effective in patients with genotypes 2 and 3 but this drug combination has not been studied in patients with decompensated cirrhosis. Thus, this regimen is not recommended for patients with decompensated cirrhosis (CPT class B or C) until further data are available.

### 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 drug combination or treatment duration is unclear, expert consultation should be sought.

**Regimens not recommended for:**
**Patients With Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; Child-Turcotte-Pugh Class B or C) <sup>i</sup>**

NOT RECOMMENDED	RATING <sup>i</sup>
Paritaprevir-based regimens	III, B
Simeprevir-based regimens	III, B
Elbasvir/grazoprevir-based regimens	III, C
Glecaprevir/pibrentasvir	III, C
Sofosbuvir/velpatasvir/voxilaprevir	III, C

Interferon should not be given to patients with decompensated cirrhosis (moderate or severe hepatic impairment, CTP class B or C) because of the potential for worsening hepatic decompensation. Limited data exist for the use of simeprevir in patients with CPT class B cirrhosis ([Modi, 2016](#)); ([Lawitz, 2017](#)). In a study of 40 patients (19 CPT class A, 21 CPT class B) with genotype 1 or 4 infection treated with simeprevir, sofosbuvir and daclatasvir for 12 weeks, the mean pharmacokinetic exposure to simeprevir at week 8 of therapy was 2.2-fold higher in patients with CPT class B versus CPT class A cirrhosis. ([Lawitz, 2017](#)). All patients achieved SVR12 but grade 3 or 4 bilirubin elevations were seen in 18% and 5% of patients, respectively, though none were associated with an ALT increase or the need for drug discontinuation. No data are available for use of the currently approved doses of elbasvir/grazoprevir, glecaprevir/pibrentasvir, or sofosbuvir/velpatasvir/voxilaprevir in patients with decompensated cirrhosis.

Recent data reported by the FDA have demonstrated that some patients with compensated cirrhosis treated with paritaprevir/ritonavir/ombitasvir ± dasabuvir may develop rapid-onset direct hyperbilirubinemia without ALT elevation within 1 to 4 weeks of starting treatment, which can lead to rapidly progressive liver failure and death. A multicenter cohort study from Israel reported 7 patients who received paritaprevir/ritonavir/ombitasvir plus dasabuvir developed decompensation within 1 to 8 weeks of starting therapy, including 1 patient who died ([Zuckerman, 2016](#)). Therefore, paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in all patients with decompensated cirrhosis due to concerns about hepatotoxicity. In addition, all patients with compensated cirrhosis receiving this regimen should be monitored for clinical signs and symptoms of hepatic decompensation and undergo hepatic laboratory testing at baseline and at least every 4 weeks while on therapy.

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