Initial Treatment of HCV Infection

Initial treatment of HCV infection includes patients with chronic hepatitis C who have not been previously treated with IFN, PEG-IFN, 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 various genotypes). Recommended regimens are those that are favored for most patients in that subgroup, based on optimal efficacy, favorable tolerability and toxicity profiles, and duration. Alternative regimens are those that are effective but have, relative to Recommended regimens, 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 a specific patient situation. Not Recommended regimens are clearly inferior compared to Recommended or Alternative regimens due to factors such as lower efficacy, unfavorable tolerability and toxicity, longer duration, and/or higher pill burden. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection. Specific considerations of 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 those with severe renal impairment or end-stage renal disease (ESRD) are addressed in other sections of the Guidance.

Recommended and Alternative regimens are listed in order of level of evidence. When several regimens are offered at the same recommendation level, they are listed in alphabetical order. Choice of regimen should be determined based on patient-specific data, including drug interactions. As always, patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response. All patients should have 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.

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Treatment-naive Genotype 1

Six highly potent DAA oral combination regimens are Recommended for patients with HCV 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 cirrhosis.

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

Approximately 10%-15% of HCV genotype 1-infected patients without prior exposure to NS5A inhibitors will have detectable HCV NS5A RASs at the population level prior to treatment. While the clinical impact of NS5A RASs remains to be fully elucidated, 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 NS5A-containing regimens (Zeuzem,

2017); (Jacobson, 2015b). These RASs include substitutions at positions M28, Q30, L31, and Y93 in genotype 1a and are found by population sequencing in roughly 5%-10% of patients. Given that baseline NS5A RASs are one of the strongest pre-treatment predictors of treatment outcome with certain regimens, testing for these RASs prior to deciding on a therapeutic course is now recommended in select situations (Zeuzem, 2015c).

The introduction of DAAs into HCV treatment regimens increased the risk of drug interactions with concomitant medications, and now with combinations of DAAs, attention to drug interactions is all the more important (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 of the regimens discussed below.

The following pages include guidance for management of treatment-naive patients with HCV Genotype 1.

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Treatment-naive Genotype 1a Without Cirrhosis

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 1a, Treatment-naive Patients, Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg); for patients in whom no baseline NS5A RASs[§] for elbasvir are detected	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
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	8 weeks	I, B
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), with weight-based ribavirin	12 weeks	I, A

Recommended and Alternative Regimens by evidence level and alphabetically for: **Genotype 1a, Treatment-naive Patients, Without Cirrhosis**		
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg)	12 weeks	I, B
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin; for patients who have baseline NS5A RASs§ for elbasvir	16 weeks	IIa, B

§ Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.
* The dose of daclatasvir may need to increase or decrease 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 HCV genotype 1a-infected, treatment-naive patients without cirrhosis, there are six regimens recommended based on comparable efficacy, as outlined above. For cirrhotic patients, some are classified as Alternative regimens because compared to the Recommended, they have longer duration, potentially reduced efficacy, and/or limited supporting data.

Elbasvir/grazoprevir

The fixed-dose combination of elbasvir (50 mg) and grazoprevir (100 mg) (hereafter elbasvir/grazoprevir) can be recommended based on data from the phase III C-EDGE trial, which assessed the efficacy and safety of elbasvir/grazoprevir for 12 weeks in treatment-naive adults (genotypes 1, 4, and 6) (Zeuzem, 2017). Patients were enrolled from 60 centers in 9 countries on 4 continents. Three hundred and eighty-two patients (91% of study cohort) receiving 12 weeks of elbasvir/grazoprevir were infected with genotype 1 (50% genotype 1a, 41% genotype 1b). The sustained virologic response rate at 12 weeks (SVR12) was 92% in treatment-naive patients with HCV genotype 1a infection (144/157) and 99% in genotype 1b (129/131) patients receiving 12 weeks of elbasvir/grazoprevir. Findings from this phase III study supported earlier phase II 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 non-cirrhotic HCV-infected 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.

Presence of certain baseline NS5A RASs significantly reduces rates of SVR12 with a 12-week course of the elbasvir/grazoprevir regimen in genotype 1a-infected patients (Zeuzem, 2017). NS5A RASs were identified at baseline 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 a larger than 5-fold shift to elbasvir was associated with the most significant reductions 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 III 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 the elbasvir/grazoprevir phase II and III trials have demonstrated SVR12 rates of 100% (6/6 patients) in genotype 1 patients with pre-treatments NS5A RASs treated with elbasvir/grazoprevir for 16/18 weeks

plus ribavirin (Jacobson, 2015b); (Thompson, 2015). Based on known inferior response in patients with presence of baseline NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for therapy with elbasvir/grazoprevir. 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.

Lack of RAS testing results or lack of access to RAS testing should not be used as a means to limit access to HCV therapy.

Ledipasvir/sofosbuvir

The fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter, ledipasvir/sofosbuvir) was approved by the FDA for the treatment of HCV genotype 1 infection in treatment-naive patients based on two registration trials: ION-1 (865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin (Afdhal, 2014a). SVR12 was 97% to 99% across all arms, with no difference in SVR based on length of treatment, use of ribavirin, or HCV genotype 1 subtype. Sixteen percent of subjects 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 rate was 93% to 95% across all 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 2 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 below 6 million IU/mL (2%; 2/123), and was the same for patients with similar baseline HCV RNA levels who received 12 weeks (2%; 2/131). This analysis was not controlled and thus limits the generalizability of this approach to clinical practice. Published real-world cohort data generally show comparable effectiveness of 8 and 12 weeks 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 African-American patients (Su, 2016); (Wilder, 2016); (O'Brien, 2014). For others, it should be done at the discretion of the practitioner with consideration taken of other potential negative prognostic factors.

Paritaprevir/ritonavir/ombitasvir + dasabuvir

The daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (PrOD) plus weight-based ribavirin was approved by the FDA for the treatment of HCV genotype 1a infection in treatment-naive patients based on three registration trials: SAPPHIRE-I (322 treatment-naive patients with genotype 1a HCV infection without cirrhosis), PEARL-IV (305 treatment-naive patients with genotype 1a without cirrhosis), and TURQUOISE-II (261 treatment-naive and -experienced patients with HCV genotype 1a and cirrhosis). The SAPPHIRE-I trial reported a high SVR12 rate (95.3%) with 12 weeks of PrOD and ribavirin (Feld, 2014). Overall, virologic failure was higher for patients with HCV genotype 1a (7 of 8 failures had genotype 1a) than patients with HCV genotype 1b (1 virologic failure). PEARL-IV was specifically designed to determine the role of PrOD with or without weight-based ribavirin for treatment-naive, HCV 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) owing to higher rates of virologic failure (7.8% vs 2%, respectively), confirming the need for weight-based ribavirin for patients with HCV genotype 1a. In 2016, an extended release formulation of PrOD was approved allowing once daily dosing (RBV when needed remains twice daily) (PrOD PI, 2017).

Simeprevir + sofosbuvir

The OPTIMIST-1 and -2 trials investigated the safety and efficacy of simeprevir (150 mg) and sofosbuvir (400 mg) in chronically infected patients with HCV genotype 1 without and with cirrhosis, respectively. In the OPTIMIST-1 study, 310

treatment-naive and -experienced patients without cirrhosis were randomly assigned to 12 vs 8 weeks of the simeprevir plus sofosbuvir regimen (Kwo, 2016). The overall SVR12 rate was 97% (150/155) versus 83% (128/155), respectively, with a statistically significantly greater relapse rate in the 8-week arm. In the 12-week arm there was no difference in SVR12; 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 presence of the baseline Q80K resistance substitution. A post-hoc analysis suggested that patients with a baseline HCV RNA level below 4 million IU/mL achieved the same SVR12 rate (96%) regardless of the length of treatment. This defined baseline HCV RNA level is different than the 6 million IU/mL defined in the ION-3 trial, suggesting these post-hoc analysis cut-offs are arbitrary and unlikely to translate to clinical practice. At this time an 8-week regimen of simeprevir and sofosbuvir cannot be recommended.

Sofosbuvir/velpatasvir

The fixed-dose combination of 12 weeks of sofosbuvir (400 mg) and velpatasvir (100 mg) (hereafter, sofosbuvir/velpatasvir) was approved by the FDA for the treatment of HCV genotype 1 infection in treatment-naive patients based on ASTRAL-1, a placebo-controlled trial that gave 12 weeks of sofosbuvir/velpatasvir to 624 participants with HCV genotypes 1, 2, 4, 5, and 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 HCV genotype (98% 1a and 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). The presence of baseline NS5A resistance-associated substitutions (at 15% cut off), reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested, did not influence SVR rate for genotype 1 (Hézode, 2016). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs present. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir group and the placebo group.

Daclatasvir + sofosbuvir

Daclatasvir in combination with sofosbuvir for the treatment of HCV genotype 1 infection can be recommended based on data from the phase III ALLY-2 trial, which assessed the efficacy and safety of daclatasvir and sofosbuvir for 12 weeks in patients coinfected with HIV and HCV (genotypes 1-4) (Wyles, 2015). One hundred twenty-three (83%) patients receiving 12 weeks of therapy in the trial were infected with HCV genotype 1. Eighty-three (54%) of these patients were treatment-naive. The sustained virologic response (SVR) rate was 96% in treatment-naive patients with HCV genotype 1a infection (n=71) receiving 12 weeks of therapy. However, only 9 treatment-naive patients had cirrhosis. Similarly, in the phase IIb study of daclatasvir and sofosbuvir (A1444040) in 88 treatment-naive patients with HCV genotype 1a infection, 21 were treated for 24 weeks (11 with ribavirin) and 67 were treated for 12 weeks (33 with ribavirin), and there were no virologic relapses. However, there were only 14 patients with cirrhosis in the 12-week and 24-week study arms (Sulkowski, 2014a). Because patients with cirrhosis were not adequately represented in these studies, the optimal duration of treatment for patients with cirrhosis remains unclear. Cohort studies of a compassionate-use program in Europe suggest that patients with cirrhosis may benefit from extension of therapy with daclatasvir and sofosbuvir to 24 weeks, with or without ribavirin (Welzel, 2016); (Pol, 2017). The phase III ALLY-1 trial investigated daclatasvir and sofosbuvir with ribavirin (initial dose of 600 mg, then titrated) in 60 patients with advanced cirrhosis (Poordad, 2016). Only 76% of patients with HCV genotype 1a (n=34) and 100% of patients with HCV genotype 1b (n=11) achieved an SVR at 12 weeks (SVR12). It is unclear how many treatment failures were among treatment-naive patients or those with CTP class A cirrhosis. More data are needed; however, owing to the risk of the emergence of resistance to nonstructural protein 5A (NS5A) inhibitor treatment at the time of failure, extending treatment to 24 weeks for all patients with HCV genotype 1a infection and cirrhosis is recommended, and the addition of ribavirin may be considered. In patients with favorable characteristics, a 12-week treatment course that includes weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) may be considered but is supported by limited data.

The safety profiles of all the Recommended regimens above appear favorable. Across numerous phase III programs, less than 1% of patients without cirrhosis discontinued treatment early and adverse events were mild. Most adverse events occurred in ribavirin-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials) but still very low.

Mixed genotypes

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

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Treatment-naive Genotype 1a with Compensated Cirrhosis

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 1a, Treatment-naive Patients, with Compensated Cirrhosis [‡]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg); for patients in whom no baseline NS5A RASs[§] for elbasvir are detected	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
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), with weight-based ribavirin [†]	24 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin; for patients in whom no Q80K substitution is detected	24 weeks	II, B
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin	24 weeks	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin; for patients who have baseline NS5A RASs[§] for elbasvir	16 weeks	IIa, B

[§] Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.
[†] Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.
[‡] For decompensated cirrhosis, please refer to the appropriate section.
*The dose of daclatasvir may need to increase or decrease 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 HCV genotype 1a-infected, treatment-naive patients without cirrhosis, there are six regimens recommended based on comparable efficacy, as outlined above. For cirrhotic patients, some are classified as Alternative regimens because compared to the Recommended, they have longer duration, potentially reduced efficacy, and/or limited supporting data.

Elbasvir/grazoprevir

The C-WORTHY trial enrolled both HCV-monoinfected and HIV/HCV-coinfected patients. Recommendations for cirrhotic patients are based on 92 (22%) patients in the phase III C-EDGE trial who had Metavir F4 disease (Zeuzem, 2017). 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 II C-WORTHY trial (Lawitz, 2015c). Presence or absence of compensated 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 rates of SVR12 with a 12-week course of the elbasvir/grazoprevir regimen in genotype 1a-infected patients (Zeuzem, 2017). NS5A RASs were identified at baseline 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 a larger than 5-fold shift to elbasvir was associated with the most significant reductions 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 III 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 the elbasvir/grazoprevir phase II and III trials have demonstrated SVR12 rates of 100% (6/6 patients) in genotype 1 patients with pre-treatments NS5A RASs treated with elbasvir/grazoprevir for 16/18 weeks plus ribavirin (Jacobson, 2015b); (Thompson, 2015). Based on known inferior response in patients with presence of baseline NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for therapy with elbasvir/grazoprevir. 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.

Lack of RAS testing results or lack of access to RAS testing should not be used as a means to limit access to HCV therapy.

Ledipasvir/sofosbuvir

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

Paritaprevir/ritonavir/ombitasvir + dasabuvir

The daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (PrOD) plus weight-based ribavirin was approved by the FDA for the treatment of HCV genotype 1a infection in treatment-naive patients based on three registration trials: SAPPHIRE-I (322 treatment-naive patients with genotype 1a HCV infection without cirrhosis), PEARL-IV (305 treatment-naive patients with genotype 1a without cirrhosis), and TURQUOISE-II (261 treatment-naive and -experienced patients with HCV genotype 1a and cirrhosis). TURQUOISE-II enrolled treatment-naive and -experienced patients (261 patients with HCV genotype 1a) with CTP class A cirrhosis to receive either 12 weeks or 24 weeks of treatment with PrOD plus ribavirin. Overall, SVR12 rates were 89% in the 12-week arm and 95% in the 24-week arm (Poordad, 2014). This difference in SVR12 rate between arms was primarily driven by patients with null response to PEG-IFN/ribavirin; there was less difference in SVR rates in the patients with cirrhosis who were naive to therapy (92% and 95%, respectively) (paritaprevir/ritonavir/ombitasvir

prescribing information); (Poordad, 2014). In 2016, an extended release formulation of PrOD was approved allowing once-daily dosing (RBV when needed remains twice daily) (PrOD PI, 2017).

In October 2015, the FDA released a warning regarding the use of the PrOD or PrO (without dasabuvir) in patients with cirrhosis. (This statement is based on our review of the limited data available from the FDA and will be updated if and when more data become available.) PrOD and PrO are contraindicated in patients with Child Turcotte Pugh (CTP) class B or C hepatic impairment (decompensated liver disease). The manufacturer's pharmacovigilance program reported rapid onset of liver injury and in some cases hepatic decompensation in patients with cirrhosis, including CTP class A compensated cirrhosis and decompensated cirrhosis, who were receiving PrOD or PrO. The liver injury and decompensating events occurred largely during the first 4 weeks of therapy and primarily involved a rapid increase in total and direct bilirubin, often associated with a concomitant increase in liver enzyme levels. In most cases, early recognition and prompt discontinuation of PrOD or PrO resulted in resolution of injury, although some patients, including at least 2 patients with CTP class A compensated cirrhosis, died or required liver transplantation. Although cirrhosis carries a 2% to 4% annual risk of hepatic decompensation, the rapid onset of hepatic decompensation and in many cases its resolution with discontinuation of treatment with PrOD or PrO is suggestive of drug-induced liver injury. Although PrOD and PrO are contraindicated in patients with CTP class B or C cirrhosis and decompensated liver disease, predictors of these events in patients with CTP class A cirrhosis are currently unclear.

For patients with CTP class A cirrhosis, the unlikely but real possibility of drug-induced liver injury should be discussed with the patient. If the decision is made to initiate treatment with PrOD or PrO, close monitoring of total and direct bilirubin and transaminase levels every 1 week or 2 weeks for the first 4 weeks is recommended to ensure early detection of drug-induced liver injury. Also, educating patients about the importance of reporting systemic symptoms such as jaundice, weakness, and fatigue is strongly recommended. The regimen should be discontinued immediately if drug-induced liver injury is detected. If a patient is already taking PrOD or PrO and is tolerating the regimen, laboratory monitoring as above without discontinuation is recommended unless there are signs or symptoms of liver injury. If heightened monitoring cannot be provided in the first 4 weeks of therapy with PrOD or PrO in patients with cirrhosis, the use of these regimens is not recommended.

Simeprevir + sofosbuvir

The OPTIMIST-2 study was a single-arm, open-label trial investigating 12 weeks of simeprevir plus sofosbuvir in 103 treatment-naive and -experienced patients with cirrhosis (Lawitz, 2016b). The overall SVR12 rate was 83% (86/103), with 88% (44/50) of treatment-naive and 79% (42/53) of treatment-experienced patients achieving SVR12. In addition, patients infected with HCV genotype 1a and 1b without the Q80K substitution had similar SVR12 rates (84% [26/31] and 92% [35/38], respectively). However, patients with HCV genotype 1a infection and the Q80K substitution had lower SVR12 rates (74% [25/34]). Thus, extending treatment to 24 weeks, with or without ribavirin, is recommended for patients with cirrhosis receiving simeprevir plus sofosbuvir to decrease the risk of relapse. At this time it is unclear whether extending treatment, with or without the addition of ribavirin, will increase efficacy in genotype 1a-infected patients with the Q80K substitution. Given the lower response rate in patients with cirrhosis, it is reasonable to avoid this regimen in patients with this baseline substitution.

Sofosbuvir/velpatasvir

The fixed-dose combination of 12 weeks of sofosbuvir (400 mg) and velpatasvir (100 mg) (hereafter, sofosbuvir/velpatasvir) was approved by the FDA for the treatment of HCV genotype 1 infection in treatment-naive patients based on ASTRAL-1, a placebo-controlled trial that gave 12 weeks of sofosbuvir/velpatasvir to 624 participants with HCV genotypes 1, 2, 4, 5, and 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 HCV genotype (98% 1a and 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). The presence of baseline NS5A resistance-associated substitutions (at 15% cut off), reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested, did not influence SVR rate for genotype 1 (Hézode, 2016). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs present. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir group and the placebo group.

Daclatasvir + sofosbuvir

Daclatasvir in combination with sofosbuvir for the treatment of HCV genotype 1 infection can be recommended based on data from the phase III ALLY-2 trial, which assessed the efficacy and safety of daclatasvir and sofosbuvir for 12 weeks in patients coinfected with HIV and HCV (genotypes 1-4) (Wyles, 2015). One hundred twenty-three (83%) patients receiving 12 weeks of therapy in the trial were infected with HCV genotype 1. Eighty-three (54%) of these patients were treatment-naive. The sustained virologic response (SVR) rate was 96% in treatment-naive patients with HCV genotype 1a infection (n=71) receiving 12 weeks of therapy. However, only 9 treatment-naive patients had cirrhosis. Similarly, in the phase IIb study of daclatasvir and sofosbuvir (A1444040) in 88 treatment-naive patients with HCV genotype 1a infection, 21 were treated for 24 weeks (11 with ribavirin) and 67 were treated for 12 weeks (33 with ribavirin), and there were no virologic relapses. However, there were only 14 patients with cirrhosis in the 12-week and 24-week study arms (Sulkowski, 2014a). Because patients with cirrhosis were not adequately represented in these studies, the optimal duration of treatment for patients with cirrhosis remains unclear. Cohort studies of a compassionate-use program in Europe suggest that patients with cirrhosis may benefit from extension of therapy with daclatasvir and sofosbuvir to 24 weeks, with or without ribavirin (Welzel, 2016); (Pol, 2017). The phase III ALLY-1 trial investigated daclatasvir and sofosbuvir with ribavirin (initial dose of 600 mg, then titrated) in 60 patients with advanced cirrhosis (Poordad, 2016). Only 76% of patients with HCV genotype 1a (n=34) and 100% of patients with HCV genotype 1b (n=11) achieved an SVR at 12 weeks (SVR12). It is unclear how many treatment failures were among treatment-naive patients or those with CTP class A cirrhosis. More data are needed; however, owing to the risk of the emergence of resistance to nonstructural protein 5A (NS5A) inhibitor treatment at the time of failure, extending treatment to 24 weeks for all patients with HCV genotype 1a infection and cirrhosis is recommended, and the addition of ribavirin may be considered. In patients with favorable characteristics, a 12-week treatment course that includes weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) may be considered but is supported by limited data.

The safety profiles of all the Recommended regimens above appear favorable. Across numerous phase III programs, less than 1% of patients without cirrhosis discontinued treatment early and adverse events were mild. Most adverse events occurred in ribavirin-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials) but still very low.

Mixed genotypes

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

Last update: April 12, 2017

Treatment-naive Genotype 1b Without Cirrhosis

Recommended Regimens by evidence level and alphabetically for:

Genotype 1b, Treatment-naive Patients, Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A

Recommended Regimens by evidence level and alphabetically for: **Genotype 1b, Treatment-naive Patients, Without Cirrhosis**		
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
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	8 weeks	I, B
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)	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg)	12 weeks	I, B
* The dose of daclatasvir may need to increase or decrease 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 HCV genotype 1b-infected, treatment-naive patients without cirrhosis, there are six regimens of comparable efficacy, as outlined above. For cirrhotic patients, some are classified as Alternative regimens, because compared to the Recommended, they have longer duration, potentially reduced efficacy, and/or limited supporting data.

There are no significant differences demonstrated to date in treatment responses to daclatasvir and sofosbuvir, ledipasvir/sofosbuvir, or sofosbuvir/velpatasvir for HCV genotype 1 subtypes, thus the supporting evidence remains the same as for HCV genotype 1a-infected patients (see Genotype 1a). In the ALLY-2 arm of daclatasvir and sofosbuvir for 12 weeks in treatment-naive patients, only 12 were 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 III trials of this regimen, there is not enough evidence to support a different approach by subtype at this time.

For elbasvir/grazoprevir, 99% of genotype 1b (129/131) patients receiving 12 weeks achieved SVR in the phase III C-EDGE trial (Zeuzem, 2015c). In contrast to genotype 1a, the presence of baseline substitutions associated with NS5A resistance did not appear to affect response to elbasvir/grazoprevir. Thus, current data do not support extending the duration or adding ribavirin in genotype 1b patients with NS5A resistance-associated substitutions. PrOD (plus ribavirin for those with cirrhosis) was approved by the FDA for the treatment of HCV genotype 1b infection in treatment-naive patients based on three registration trials: SAPPHIRE-I (151 treatment-naive patients with HCV genotype 1b and without cirrhosis), PEARL-III (419 treatment-naive patients, all with genotype 1b and without cirrhosis), and TURQUOISE-II (119 treatment-naive and -experienced patients with genotype 1b with cirrhosis). SAPPHIRE-I reported a high SVR12 rate (98%) with 12 weeks of PrOD and ribavirin in patients with HCV genotype 1b (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 PrOD in treatment-naive patients with HCV genotype 1b without cirrhosis (Ferenci, 2014). SVR12 rate was 99% in both arms, confirming that there is no added benefit from the use of weight-based ribavirin for patients without cirrhosis who have HCV genotype 1b infection. GARNET, a phase 3b single-arm study of 163 genotype 1b patients without cirrhosis, demonstrated a 98% SVR rate with an 8-week duration of PrOD. When considering the generalizability of these results, it is important to note that 91% of the GARNET participants had fibrosis stage F0-F2, 93% had HCV RNA levels <6,000,000 IU/mL, and 96% were white. In addition, 2 of the 15 patients with fibrosis stage F3 experienced virologic

relapse, suggesting that if used, an 8-week strategy should be reserved for those with early stage fibrosis (Welzel, 2016).

To date, there is no measurable difference demonstrated in treatment response to simeprevir plus sofosbuvir for HCV genotype 1 subtypes (with the exception of patients with genotype 1a with cirrhosis who also have the baseline Q80K substitution described above), thus the supporting evidence remains the same as for HCV genotype 1a-infected patients (see Genotype 1a).

The safety profiles to date of all recommended regimens above appear favorable. Across numerous phase III programs, less than 1% of patients without cirrhosis discontinued treatment early and adverse events were mild. Most adverse events occurred in ribavirin-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials) but still very low.

Mixed genotypes

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

Last update: April 12, 2017

Treatment-naive Genotype 1b with Compensated Cirrhosis

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 1b, Treatment-naive Patients, with Compensated Cirrhosis ‡

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
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) †	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin	24 weeks	IIa, B
Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin	24 weeks	IIa, B

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 1b, Treatment-naive Patients, with Compensated Cirrhosis ‡

† Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.
‡ For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease 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 HCV genotype 1b-infected, treatment-naive patients without cirrhosis, there are six regimens of comparable efficacy, as outlined above. For cirrhotic patients, some are classified as Alternative regimens, because compared to the Recommended, they have longer duration, potentially reduced efficacy, and/or limited supporting data.

There are no significant differences demonstrated to date in treatment responses to daclatasvir and sofosbuvir, ledipasvir/sofosbuvir, or sofosbuvir/velpatasvir for HCV genotype 1 subtypes, thus the supporting evidence remains the same as for HCV genotype 1a-infected patients (see Genotype 1a). In the ALLY-2 arm of daclatasvir and sofosbuvir for 12 weeks in treatment-naive patients, only 12 were 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 III trials of this regimen, there is not enough evidence to support a different approach by subtype at this time.

For elbasvir/grazoprevir, 99% of genotype 1b (129/131) patients receiving 12 weeks achieved SVR in the phase III C-EDGE trial (Zeuzem, 2015c). In contrast to genotype 1a, the presence of baseline substitutions associated with NS5A resistance did not appear to affect response to elbasvir/grazoprevir. Thus, current data do not support extending the duration or adding ribavirin in genotype 1b patients with NS5A resistance-associated substitutions. PrOD (plus ribavirin for those with cirrhosis) was approved by the FDA for the treatment of HCV genotype 1b infection in treatment-naive patients based on three registration trials: SAPPHIRE-I (151 treatment-naive patients with HCV genotype 1b and without cirrhosis), PEARL-III (419 treatment-naive patients, all with genotype 1b and without cirrhosis), and TURQUOISE-II (119 treatment-naive and -experienced patients with genotype 1b with cirrhosis). SAPPHIRE-I reported a high SVR12 rate (98%) with 12 weeks of PrOD and ribavirin in patients with HCV genotype 1b (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 PrOD in treatment-naive patients with HCV genotype 1b without cirrhosis (Ferenci, 2014). SVR12 rate was 99% in both arms, confirming that there is no added benefit from the use of weight-based ribavirin for patients without cirrhosis who have HCV genotype 1b infection. TURQUOISE-II enrolled treatment-naive and -experienced patients with CTP class A cirrhosis to receive either 12 weeks or 24 weeks of treatment with PrOD 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 HCV genotype 1b and cirrhosis, the TURQUOISE-III study evaluated the safety and efficacy of PrOD without ribavirin for 12 weeks in patients with HCV 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 109/L, and 17% with albumin levels <3.5 g/dL) were enrolled. All patients completed treatment, and all patients achieved an SVR12. On the basis of this study, treating patients with HCV genotype 1b with PrOD but without ribavirin is recommended, regardless of prior treatment experience or presence of cirrhosis (Feld, 2016). GARNET, a phase 3b single-arm study of 163 genotype 1b patients without cirrhosis, demonstrated a 98% SVR rate with an 8-week duration of PrOD. When considering the generalizability of these results, it is important to note that 91% of the GARNET participants had fibrosis stage F0-F2, 93% had HCV RNA levels <6,000,000 IU/mL, and 96% were white. In addition, 2 of the 15 patients with fibrosis stage F3 experienced virologic relapse, suggesting that if used, an 8-week strategy should be reserved for those with early stage fibrosis (Welzel, 2016).

To date, there is no measurable difference demonstrated in treatment response to simeprevir plus sofosbuvir for HCV genotype 1 subtypes (with the exception of patients with genotype 1a with cirrhosis who also have the baseline Q80K substitution described above), thus the supporting evidence remains the same as for HCV genotype 1a-infected patients (see Genotype 1a).

The safety profiles to date of all recommended regimens above appear favorable. Across numerous phase III programs, less than 1% of patients without cirrhosis discontinued treatment early and adverse events were mild. Most adverse events occurred in ribavirin-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials) but still very low.

Mixed genotypes

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

Last update: April 12, 2017

Treatment-naive Genotype 2

The following pages include guidance for management of treatment-naive patients with HCV Genotype 2.

- Treatment-naive Genotype 2 Without Cirrhosis
- Treatment-naive Genotype 2 with Compensated Cirrhosis

Last update: April 12, 2017

Treatment-naive Genotype 2 Without Cirrhosis

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 2, Treatment-naive Patients, Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg)	12 weeks	IIa, B

* The dose of daclatasvir may need to increase or decrease 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.

Sofosbuvir/velpatasvir

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

Daclatasvir + sofosbuvir

Daclatasvir with sofosbuvir for 12 weeks was approved by the FDA for the treatment of HCV genotype 3 infection in patients without and with cirrhosis. Although daclatasvir with sofosbuvir was not approved for the treatment of HCV genotype 2 infection, daclatasvir maintains adequate activity against HCV 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 rates of SVR in treatment-naive patients with HCV 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 HCV genotype 2-infected patients who would benefit from extending treatment. For patients who require treatment but cannot tolerate sofosbuvir/velpatasvir, a regimen of daclatasvir with sofosbuvir for 12 weeks is reasonable.

Mixed genotypes

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

Last update: April 12, 2017

Treatment-naive Genotype 2 with Compensated Cirrhosis

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 2, Treatment-naive Patients, with Compensated Cirrhosis ‡

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) ‡	16 weeks to 24 weeks	IIa, B

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 2, Treatment-naive Patients, with Compensated Cirrhosis ‡

‡ For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease 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.

Sofosbuvir/velpatasvir

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

Daclatasvir + sofosbuvir

Daclatasvir with sofosbuvir for 12 weeks was approved by the FDA for the treatment of HCV genotype 3 infection in patients without and with cirrhosis. Although daclatasvir with sofosbuvir was not approved for the treatment of HCV genotype 2 infection, daclatasvir maintains adequate activity against HCV 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 rates of SVR in treatment-naive patients with HCV 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 HCV genotype 2-infected patients who would benefit from extending treatment. For patients who require treatment but cannot tolerate sofosbuvir/velpatasvir, a regimen of daclatasvir with sofosbuvir for 12 weeks is reasonable.

Mixed genotypes

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

Last update: April 12, 2017

Treatment-naive Genotype 3

The following pages include guidance for management of treatment-naive patients with HCV Genotype 3.

- Treatment-naive Genotype 3 Without Cirrhosis

- Treatment-naive Genotype 3 with Compensated Cirrhosis

Last update: April 12, 2017

Treatment-naive Genotype 3 Without Cirrhosis

Recommended Regimens by evidence level and alphabetically for:

Genotype 3, Treatment-naive Patients, Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

* The dose of daclatasvir may need to increase or decrease 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.

Daclatasvir + sofosbuvir

Daclatasvir with sofosbuvir for 12 weeks was approved by the FDA for treatment of HCV genotype 3 infection. The recommendation is based on ALLY-3, a phase III study of the once-daily NS5A inhibitor daclatasvir plus sofosbuvir for 12 weeks; 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, and in treatment-naive patients with cirrhosis (Metavir F4), 58% achieved SVR12 (Nelson, 2015). This suggests 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% versus 86% when daclatasvir and sofosbuvir were used for 12 weeks and 24 weeks in HCV genotype 3-infected patients with cirrhosis, respectively. The role of ribavirin could not be clarified, as only 4 patients received daclatasvir plus sofosbuvir and ribavirin for 12 weeks, all or which achieved SVR12. SVR12 was comparable between the 24-week arms irrespective of the addition of ribavirin (85.9% [116/135] without compared to 81.3% [39/48] with ribavirin). SVR12 rates were also higher in those with compensated Child-Pugh A cirrhosis (85%-90% compared to 70.6% in Child B/C). Again the addition of ribavirin did not increase SVR12 rates in the 24-week arms (Hézode, 2017). 73% of patients were treatment-experienced, however earlier data suggested that SVR12 rates were higher in treatment-naive patients (91%-100%) compared to experienced (81%-82%). SVR12 rates were similar in those that received ribavirin (88%, 29/33) and those that did not (86%, 42/49) (Hézode, 2017).

Presence of baseline NS5A RASs significantly reduces rates of SVR12 with a 12-week course of daclatasvir plus sofosbuvir in genotype 3-infected patients. In analysis of 175 subjects infected with HCV genotype 3 and nucleotide sequence data in the ALLY-3 trial, the presence of a NS5A Y93H substitution was associated with a reduced SVR12 rate; 54% (7/13) compared to 92% (149/162). Although the small numbers make interpretation difficult, only 7% (13/175) had NS5A Y93H substitution, all of which were subgenotype 3a. SVR rates were numerically lower in those with both cirrhosis and Y93H. In non-cirrhotic subjects with Y93H, 67% (6/9) achieved SVR12 compared to 98% (125/128) of those non-cirrhotic 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 substitution (Daclatasvir PI, 2016). Substitutions at A30K, L31F, L31I in genotype 3a replicon are associated with reduced daclatasvir susceptibility (Daclatasvir PI, 2016). In the ALLY-3 trial, subjects with A30K and without cirrhosis achieved 100% SVR12 (9/9), however those with cirrhosis had lower SVR12 rates (1/5) (Nelson, 2015). The impact of this single substitution is difficult to discern as 2/5 had compound substitutions with Y93H. Pending further data on optimal therapy in the setting of baseline Y93 substitution, the addition of ribavirin for patients with

cirrhosis is recommended.

Sofosbuvir/velpatasvir

Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of HCV genotype 3 infection in patients with and without cirrhosis. ASTRAL-3 demonstrated superiority of 12 weeks of sofosbuvir/velpatasvir to 24 weeks sofosbuvir plus ribavirin in 552 treatment-naive and -experienced subjects with and without cirrhosis (Foster, 2015a). In treatment-naive, non-cirrhotic subjects, SVR12 rates were 98% (160/163) compared to 90% (141/156), respectively. In those with cirrhosis SVR12 was 93% (40/43) compared to 73% (33/45), respectively. Of the 250 subjects that received sofosbuvir/velpatasvir 43 (16%) had baseline NS5A RASs; of which 88% achieved SVR12 compared to 97% without baseline substitutions. 84% (21/25) with Y93H achieved SVR12. Pending further data on optimal therapy in the setting of baseline Y93 substitution, the addition of ribavirin for patients with cirrhosis is recommended.

Elbasvir/grazoprevir + sofosbuvir

C-SWIFT investigated the efficacy of triple therapy with the daily fixed-dose combination of elbasvir/grazoprevir and sofosbuvir (400 mg) for 8 weeks to 12 weeks in genotype 3 treatment-naive patients with and without compensated cirrhosis. 93% (14/15) of non-cirrhotic patients achieved SVR12 with 8 weeks and 100% (14/14) with 12 weeks of this combination. 91% (10/11) compensated cirrhotic subjects achieved SVR12 with 12 weeks of therapy (Poordad, 2016).

Mixed genotypes

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

Last update: April 12, 2017

Treatment-naive Genotype 3 with Compensated Cirrhosis

Recommended Regimens by evidence level and alphabetically for:

Genotype 3, Treatment-naive Patients, with Compensated Cirrhosis ‡

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) ¶	12 weeks	I, A
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin ¶	24 weeks	IIa, B

‡ For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease 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 by evidence level and alphabetically for:

Genotype 3, Treatment-naive Patients, with Compensated Cirrhosis [‡]

[¶] RAS testing for Y93H is recommended for cirrhotic patients and ribavirin should be included in regimen if present.

Daclatasvir + sofosbuvir

Daclatasvir with sofosbuvir for 12 weeks was approved by the FDA for treatment of HCV genotype 3 infection. The recommendation is based on ALLY-3, a phase III study of the once-daily NS5A inhibitor daclatasvir plus sofosbuvir for 12 weeks; 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, and in treatment-naive patients with cirrhosis (Metavir F4), 58% achieved SVR12 (Nelson, 2015). This suggests 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% versus 86% when daclatasvir and sofosbuvir were used for 12 weeks and 24 weeks in HCV genotype 3-infected patients with cirrhosis, respectively. The role of ribavirin could not be clarified, as only 4 patients received daclatasvir plus sofosbuvir and ribavirin for 12 weeks, all or which achieved SVR12. SVR12 was comparable between the 24-week arms irrespective of the addition of ribavirin (85.9% [116/135] without compared to 81.3% [39/48] with ribavirin). SVR12 rates were also higher in those with compensated Child-Pugh A cirrhosis (85%-90% compared to 70.6% in Child B/C). Again the addition of ribavirin did not increase SVR12 rates in the 24-week arms (Hézode, 2017). 73% of patients were treatment-experienced, however earlier data suggested that SVR12 rates were higher in treatment-naive patients (91%-100%) compared to experienced (81%-82%). SVR12 rates were similar in those that received ribavirin (88%, 29/33) and those that did not (86%, 42/49) (Hézode, 2017).

The exact duration of therapy for a treatment-naive genotype 3 patient with compensated cirrhosis is not known. The phase III study, ALLY3-+, investigated the combination of daclatasvir plus sofosbuvir and ribavirin for 12 weeks or 16 weeks in treatment-naive and -experienced genotype 3 patients with both stage 3 and compensated cirrhosis. Overall SVR12 rates were 86% with cirrhosis, the majority of which were treatment experienced. Extending the duration to 16 weeks did not have a strong impact with 88% (15/17) achieving SVR12 with 12 weeks and 89% (16/18) achieving SVR12 with 16 weeks. All 14 patients with stage 3 disease achieved SVR12 irrespective of treatment duration (Leroy, 2016).

Presence of baseline NS5A RASs significantly reduces rates of SVR12 with a 12-week course of daclatasvir plus sofosbuvir in genotype 3-infected patients. In analysis of 175 subjects infected with HCV genotype 3 and nucleotide sequence data in the ALLY-3 trial, the presence of a NS5A Y93H substitution was associated with a reduced SVR12 rate; 54% (7/13) compared to 92% (149/162). Although the small numbers make interpretation difficult, only 7% (13/175) had NS5A Y93H substitution, all of which were subgenotype 3a. SVR rates were numerically lower in those with both cirrhosis and Y93H. In non-cirrhotic subjects with Y93H, 67% (6/9) achieved SVR12 compared to 98% (125/128) of those non-cirrhotic 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 substitution (Daclatasvir PI, 2016). Substitutions at A30K, L31F, L31I in genotype 3a replicon are associated with reduced daclatasvir susceptibility (Daclatasvir PI, 2016). In the ALLY-3 trial, subjects with A30K and without cirrhosis achieved 100% SVR12 (9/9), however those with cirrhosis had lower SVR12 rates (1/5) (Nelson, 2015). The impact of this single substitution is difficult to discern as 2/5 had compound substitutions with Y93H. Pending further data on optimal therapy in the setting of baseline Y93 substitution, the addition of ribavirin for patients with cirrhosis is recommended.

Additional real-world studies support the use of this regimen for treatment-naive, genotype-3 infected patients with advanced liver disease (Welzel, 2016).

Sofosbuvir/velpatasvir

Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the

treatment of HCV genotype 3 infection in patients with and without cirrhosis. ASTRAL-3 demonstrated superiority of 12 weeks of sofosbuvir/velpatasvir to 24 weeks sofosbuvir plus ribavirin in 552 treatment-naive and -experienced subjects with and without cirrhosis (Foster, 2015a). In those with cirrhosis SVR12 was 93% (40/43) compared to 73% (33/45), respectively. Of the 250 subjects that received sofosbuvir/velpatasvir 43 (16%) had baseline NS5A RASs; of which 88% achieved SVR12 compared to 97% without baseline substitutions. 84% (21/25) with Y93H achieved SVR12. Pending further data on optimal therapy in the setting of baseline Y93 substitution, the addition of ribavirin for patients with cirrhosis is recommended.

Elbasvir/grazoprevir + sofosbuvir

C-SWIFT investigated the efficacy of triple therapy with the daily fixed-dose combination of elbasvir/grazoprevir and sofosbuvir (400 mg) for 8 weeks to 12 weeks in genotype 3 treatment-naive patients with and without compensated cirrhosis. 93% (14/15) of non-cirrhotic patients achieved SVR12 with 8 weeks and 100% (14/14) with 12 weeks of this combination. 91% (10/11) compensated cirrhotic subjects achieved SVR12 with 12 weeks of therapy (Poordad, 2016).

Mixed genotypes

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

Last update: April 12, 2017

Treatment-naive Genotype 4

The following pages include guidance for management of treatment-naive patients with HCV Genotype 4.

- Treatment-naive Genotype 4 Without Cirrhosis
- Treatment-naive Genotype 4 with Compensated Cirrhosis

Last update: April 12, 2017

Treatment-naive Genotype 4 Without Cirrhosis

Recommended Regimens by evidence level and alphabetically for:

Genotype 4, Treatment-naive Patients, Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin	12 weeks	I, A

Recommended Regimens by evidence level and alphabetically for: **Genotype 4, Treatment-naive Patients, Without Cirrhosis**		
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B

Paritaprevir/ritonavir/ombitasvir

PEARL-I was an open-label phase IIb study that included a cohort of 86 treatment-naive patients with HCV genotype 4 infection without cirrhosis who received 12 weeks of the daily fixed-dose combination of paritaprevir/ritonavir/ombitasvir (PrO) with or without weight-based ribavirin. SVR12 rates were 100% (42/42) in the group receiving ribavirin 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, in its first phase, randomized 120 treatment-naive and -experienced patients with genotype 4 HCV and compensated cirrhosis to receive 12 weeks or 16 weeks of paritaprevir/ritonavir/ombitasvir (PrO) 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 ongoing AGATE-II trial offered 100 treatment-naive and -experienced non-cirrhotic patients with genotype 4, PrO plus weight-based ribavirin for 12 weeks. The SVR12 was 94%. These data continue to support the use of PrO plus ribavirin for 12 weeks in treatment-experienced genotype 4 patients (Esmat, 2015).

Sofosbuvir/velpatasvir

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

Elbasvir/grazoprevir

Sixty-six treatment-naive genotype 4 patients have been treated with daily elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks with (n=10) and without (n=56) weight-based ribavirin in the phase 2/3 clinical program. 9.1% (n=6) were cirrhotic and 42.4% (n=28) had HIV/HCV coinfection. Overall 97% (64/66) achieved SVR12. There was 1 treatment failure and 1 subject was lost to follow-up. The impact of ribavirin could not be assessed, however the addition of ribavirin numerically increased the SVR12 rates in treatment-experienced subjects. Baseline RASs and subgenotype did not appear to impact SVR12 rates (Asselah, 2015).

Ledipasvir/sofosbuvir

The SYNERGY trial was an open-label study evaluating 12 weeks of ledipasvir/sofosbuvir in 21 HCV 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. All of the 20 patients who completed treatment achieved an 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 HCV genotype 4-infected, treatment-naive patients (only 1 with cirrhosis) with an SVR12 rate of 95% (21/22) (Abergel, 2016). These two pilot studies support the use of this regimen in patients with HCV genotype 4 infection.

Mixed genotypes

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

Last update: April 12, 2017

Treatment-naive Genotype 4 with Compensated Cirrhosis

Recommended Regimens by evidence level and alphabetically for:

Genotype 4, Treatment-naive Patients, with Compensated Cirrhosis [‡]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin[†]	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B

[†] Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.
[‡] For decompensated cirrhosis, please refer to the appropriate section.

Paritaprevir/ritonavir/ombitasvir

PEARL-I was an open-label phase IIb study that included a cohort of 86 treatment-naive patients with HCV genotype 4 infection without cirrhosis who received 12 weeks of the daily fixed-dose combination of paritaprevir/ritonavir/ombitasvir (PrO) with or without weight-based ribavirin. SVR12 rates were 100% (42/42) in the group receiving ribavirin 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, in its first phase, randomized 120 treatment-naive and -experienced patients with genotype 4 HCV and compensated cirrhosis to receive 12 weeks or 16 weeks of paritaprevir/ritonavir/ombitasvir (PrO) 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 ongoing AGATE-II trial offered 100 treatment-naive and -experienced non-cirrhotic patients with genotype 4, PrO 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 PrO plus weight-based ribavirin. The SVR12 rate from the 12-week arm was 97%. These data continue to support the use of PrO plus ribavirin for 12 weeks in treatment-experienced genotype 4 patients, including those with cirrhosis (Esmat, 2015).

Sofosbuvir/velpatasvir

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

Elbasvir/grazoprevir

Sixty-six treatment-naive genotype 4 patients have been treated with daily elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks with (n=10) and without (n=56) weight-based ribavirin in the phase 2/3 clinical program. 9.1% (n=6) were cirrhotic and 42.4% (n=28) had HIV/HCV coinfection. Overall 97% (64/66) achieved SVR12. There was 1 treatment failure and 1 subject was lost to follow-up. The impact of ribavirin could not be assessed, however the addition of ribavirin numerically increased the SVR12 rates in treatment-experienced subjects. Baseline RASs and subgenotype did not appear to impact SVR12 rates (Asselah, 2015).

Ledipasvir/sofosbuvir

The SYNERGY trial was an open-label study evaluating 12 weeks of ledipasvir/sofosbuvir in 21 HCV 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. All of the 20 patients who completed treatment achieved an 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 HCV genotype 4-infected, treatment-naive patients (only 1 with cirrhosis) with an SVR12 rate of 95% (21/22) (Abergel, 2016). These two pilot studies support the use of this regimen in patients with HCV genotype 4 infection.

Mixed genotypes

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

Last update: April 12, 2017

Treatment-naive Genotype 5 or 6

Recommended Regimens by evidence level and alphabetically for:

Genotype 5 or 6, Treatment-naive Patients, with and Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B

Sofosbuvir/velpatasvir

Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of HCV genotype 5 and 6 infection in patients with and without cirrhosis (Feld, 2015). ASTRAL-1 included 24 genotype 5 treatment-naive subjects with and without cirrhosis, 23 of whom achieved SVR12 (96%), and 38 genotype 6 treatment-naive subjects with and without cirrhosis, all of whom achieved SVR12 (100%).

Ledipasvir/sofobuvir

Although there are limited data on patients with HCV genotype 5 infection, the in vitro activity for sofobuvir and ledipasvir is 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 HCV 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 of whom achieved SVR12.

Ledipasvir has in vitro activity against most HCV genotype 6 subtypes (except for 6e) (Wong, 2013); (Kohler, 2014). A small, two-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 HCV genotype 6 infection. Twenty-five patients (92% were treatment-naive) who were primarily Asian (88%) had infection from seven different subtypes (32%, 6a; 24%, 6e; 12%, 6l; 8%, 6m; 12%, 6p; 8%, 6q; 4%, 6r). Two patients (8%) had cirrhosis. The SVR12 rate was 96% (24/25), and the 1 patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events (Gane, 2015).

Elbasvir/grazoprevir

C-SCAPE evaluated the efficacy and safety of 12 weeks of elbasvir (50 mg)/grazoprevir (100 mg) with or without weight-based ribavirin for 12 weeks in treatment-naive, non-cirrhotic genotype 2, 4, 5, and 6 patients. Eight genotype 5 and eight genotype 6 patients were included in this trial. In patients with HCV genotype 5 infection, administration of a 12-week regimen of elbasvir (50 mg)/grazoprevir (100 mg) plus ribavirin appears to be more active (SVR 100%, 4/4) than the same regimen without ribavirin (SVR12 25%, 1/4). Administration of a 12-week regimen of elbasvir (50 mg)/grazoprevir (100 mg) ± ribavirin to non-cirrhotic, treatment-naive patients with HCV genotype 6 infection achieved an SVR12 of 75% irrespective of the addition of ribavirin (Brown, 2015).

C-EDGE evaluated 10 treatment-naive genotype 6 patients who were treated with 12 weeks of the fixed-dose combination therapy, elbasvir (50 mg)/grazoprevir (100 mg). Eight of 10 (80%) achieved SVR12 (Zeuzem, 2015f).

Mixed genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for

mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

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