



## Patients with Renal Impairment

HCV is independently associated with the development of chronic kidney disease (CKD) ([Rogal, 2016](#)); ([Fabrizi, 2015](#)). A meta-analysis published in 2015 demonstrated that chronic HCV infection was associated with a 51% increase in the risk of proteinuria and a 43% increase in the incidence of CKD ([Fabrizi, 2015](#)). There is also a higher risk of progression to end-stage renal disease (ESRD) in persons with chronic HCV and CKD, and an increased risk of all-cause mortality in persons on dialysis ([Lee, 2014](#)); ([Fabrizi, 2012](#)).

Recommendations for Patients With CKD Stage <sup>a</sup> 1, 2, or 3	
RECOMMENDED	RATING 
<p>No dose adjustment is required when using:</p> <ul style="list-style-type: none"> <li>• Daclatasvir (60 mg)<sup>b</sup></li> <li>• Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)</li> <li>• Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)<sup>c</sup></li> <li>• Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</li> <li>• Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</li> <li>• Simeprevir (150 mg)</li> <li>• Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)</li> <li>• Sofosbuvir (400 mg)</li> </ul>	I, A
<p><sup>a</sup> Chronic kidney disease (CKD) stages: 1 = normal (eGFR &gt;90 mL/min); 2 = mild CKD (eGFR 60-89 mL/min); 3 = moderate CKD (eGFR 30-59 mL/min); 4 = severe CKD (eGFR 15-29 mL/min); 5 = end-stage CKD (eGFR &lt;15 mL/min)</p> <p><sup>b</sup> Refer to the prescribing information and the section on <a href="#">HIV/HCV coinfection</a> for patients on antiretroviral therapy.</p> <p><sup>c</sup> This is a 3-tablet coformulation. Please refer to the prescribing information.</p>	

Recommended regimens listed by evidence level and alphabetically for:			
Patients With CKD Stage <sup>a</sup> 4 or 5 (eGFR <30 mL/min or End-Stage Renal Disease)			
RECOMMENDED	GENOTYPE	DURATION	RATING 
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	1a, 1b, 4	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup>	1, 2, 3, 4, 5, 6	8 to 16 weeks <sup>c</sup>	I, B <sup>c</sup>
<p><sup>a</sup> Chronic kidney disease (CKD) stages: 1 = normal (eGFR &gt;90 mL/min); 2 = mild CKD (eGFR 60-89 mL/min); 3 = moderate CKD (eGFR 30-59 mL/min); 4 = severe CKD (eGFR 15-29 mL/min); 5 = end-stage CKD (eGFR &lt;15 mL/min)</p> <p><sup>b</sup> This is a 3-tablet coformulation. Please refer to the prescribing information.</p> <p><sup>c</sup> Patients in this group should be treated as would patients without CKD. Duration of glecaprevir/pibrentasvir should be based on presence of cirrhosis and prior treatment experience (please refer to appropriate section). As such, strength of rating may be lower for certain subgroups.</p>			

## Recommended Regimens

### Elbasvir/Grazoprevir

The C-SURFER trial evaluated the safety and efficacy of 12 weeks of the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) versus placebo among genotype 1-infected patients with CKD stage 4 or 5 (eGFR <30 mL/min). The initial study randomized eligible patients to immediate or deferred treatment with elbasvir/grazoprevir. The delayed treatment arm initially received placebo and was later treated with elbasvir/grazoprevir. Notably, both elbasvir and grazoprevir are primarily hepatically metabolized and undergo minimal renal elimination.

The data for the immediate treatment arm have been published ([Roth, 2015](#)). Seventy-five percent of the study participants were on hemodialysis, and 45% were African American. A small number of patients with compensated cirrhosis were included. The SVR12 rates (intention-to-treat [ITT] and modified intention-to-treat [mITT] analysis) were 94% and 99%, respectively. There were no changes in hemoglobin or other adverse events, or erythropoietin use in the treatment groups compared to placebo. None of the genotype 1a-infected patients with baseline NS5A RASs experienced viral relapse. The only reported relapse occurred in a patient with genotype 1b infection. The basis for the lack of impact of NS5A RASs on SVR rates in this population is unclear but may relate to the moderately increased area under the curve (AUC) with grazoprevir and elbasvir observed in patients with stage 4/5 CKD ([Elbasvir and grazoprevir PI, 2016](#)).

Based on these data, daily fixed-dose elbasvir/grazoprevir is recommended for the treatment of genotype 1 infection in patients with severely compromised renal function. While C-SURFER did not evaluate patients with genotype 4 infection, it is likely that the high efficacy of elbasvir/grazoprevir in genotype 1 and 4 infection in persons with normal renal function can be extrapolated to genotype 4-infected persons with CKD stage 4/5. Treatment with elbasvir/grazoprevir in persons with CKD has been shown to be cost-effective in the United States ([Elbasha, 2016](#)).

### Glecaprevir/Pibrentasvir

The EXPEDITION-4 trial evaluated the safety and efficacy of 12 weeks of the pangenotypic NS3/NS4A protease inhibitor glecaprevir and the pangenotypic NS5A inhibitor pibrentasvir for genotype 1, 2, 3, 4, 5, or 6 infection ([Gane, 2016b](#)). This open-label study enrolled treatment-naïve and -experienced patients (previous interferon or peginterferon ± ribavirin, or sofosbuvir and ribavirin ± peginterferon) with CKD stage 4 or 5, including hemodialysis dependence. Baseline characteristics of the 104 patients enrolled in the study were: 76% male; 25% black; 19% compensated cirrhosis; 40% treatment experienced; and 82% hemodialysis dependent. The genotype distribution was: 22% genotype 1a; 28% genotype 1b; 16% genotype 2; 11% genotype 3; 19% genotype 4; 1% genotype 5; and 1% genotype 6. In the study, the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120mg) was administered as three 100 mg/40 mg fixed-dose combination pills.

The study reported ITT and mITT SVR12 rates of 98% and 100%, respectively. There were no virologic failures. Two patients did not achieve SVR12; 1 patient discontinued the study due to diarrhea in the context of recent gastrointestinal bleeding and the other experienced a cerebral hemorrhage due to uncontrolled hypertension (had achieved SVR4). Adverse events included pruritus (20%), fatigue (14%), and nausea (12%). There were no serious adverse events related to the study drugs, and there were no grade 4 laboratory abnormalities reported.

The EXPEDITION-4 trial supports the efficacy and safety of glecaprevir/pibrentasvir in patients with CKD and ESRD. The recommended duration of therapy is the same as for patients without CKD.

### Sofosbuvir-Based Regimens

Safe and effective doses of sofosbuvir in persons with an eGFR <30 mL/min have not been established. However, there is accumulating evidence on use of sofosbuvir-based regimens in those with an eGFR <30 mL/min ([Desnoyer, 2016](#)).

The HCV-TARGET study is an ongoing prospective, observational cohort study that evaluates the use of direct-acting antiviral agents across clinical practices in North America and Europe. The study reported the safety and efficacy of sofosbuvir-containing regimens in patients with mild to severe renal dysfunction (eGFR groups: <30 mL/min; 31-45 mL/min; 46-60 mL/min; and >60 mL/min) ([Saxena, 2016](#)). The patients received different regimens that included sofosbuvir (peginterferon/ribavirin plus sofosbuvir; simeprevir and sofosbuvir ± ribavirin; and sofosbuvir plus ribavirin). Overall, the regimens were well tolerated with no increased discontinuation among patients with low eGFRs. The SVR12 rates were similar across the eGFR groups. Notably, there was progressive deterioration of renal function and related symptoms in patients with an eGFR <30 mL/min, suggesting the need for close monitoring of these patients. In summary, patients with low baseline renal function have a higher frequency of anemia, worsening renal dysfunction, and more severe adverse events, but treatment responses remain high and comparable to those without renal impairment.

### **Daclatasvir, Elbasvir, Grazoprevir, Ledipasvir, and Simeprevir**

Daclatasvir, elbasvir, grazoprevir, ledipasvir, and simeprevir are primarily hepatically metabolized and undergo minimal renal elimination. While exposures to many of these agents are higher in severe renal impairment—presumably due to effects of uremic toxins, parathyroid hormone, and/or cytokines on hepatic metabolism—they do not require dose adjustments in the setting of renal impairment.

### **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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