

Therapeutic Class Overview

Hepatitis C Direct-Acting Antivirals

INTRODUCTION

- The hepatitis C virus (HCV) is an enveloped ribonucleic acid (RNA) virus that is transmitted through exposure to infected blood (*Centers for Disease Control and Prevention [CDC] 2018*).
 - Approximately 75 to 85% of people infected with HCV will develop chronic infection.
 - The CDC estimates that 3.5 million persons in the U.S. have chronic hepatitis C (CHC).
 - Chronic HCV infection can lead to the development of active liver disease, including cirrhosis and liver cancer. It is one of the most common indications for liver transplant (*CDC 2018*).
- There are 6 major genotypes of HCV, numbered 1 to 6. Genotypes are further divided into subtypes, designated by a letter (*Gower et al 2014*).
 - Genotype 1 is the most prevalent HCV genotype globally (~46% of cases), followed by genotype 3 (~22 to 30% of cases). Genotypes 2, 4, and 6 represent 22.8% of cases combined; genotype 5 represents less than 1% of cases worldwide (*Messina et al 2015, Gower et al 2014*).
 - In the U.S., the prevalence of genotype 1a, 1b, 2, 3, 4, and 6 is 46.2%, 26.3%, 10.7%, 8.9%, 6.3%, and 1.1%, respectively (*Gower et al 2014*).
- Due to the slow evolution of chronic infection, it is difficult to directly demonstrate whether treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virologic parameters. The primary goal of therapy for hepatitis C is eradication of the virus. There are a number of different terms in use that are relevant to monitoring response to therapy:
 - Rapid virologic response (RVR): undetectable viral load at week 4
 - Early virologic response (EVR): at least a 2-log reduction in viral load by week 12 (partial EVR) or undetectable viral load by week 12 (complete EVR)
 - End-of-treatment response (ETR): undetectable viral load at the end of treatment
 - Sustained virologic response (SVR): undetectable viral load at the conclusion of therapy and 24 weeks after the conclusion of therapy (*Hepatitis C Support Project [HCSP] Fact Sheet 2015*).
- Obtaining an SVR is associated with a 97 to 100% chance of being HCV RNA negative during long-term follow-up. Furthermore, achieving an SVR is associated with decreased mortality, rates of hepatocellular carcinoma, liver-related complications, and the need for liver transplant. Thus, success at obtaining SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications. Some trials report SVR at 12 weeks (SVR12) in addition to or instead of at 24 weeks (SVR24). There is a high degree of concordance between SVR12 and SVR24, and SVR12 is also considered an appropriate endpoint (*Chen et al 2013*).
- Over recent years, research has focused on oral HCV agents that act directly on viral targets. These direct-acting antivirals (DAAs) are stratified into 4 major categories: NS3/4A protease inhibitors, NS5B nucleoside polymerase inhibitors, NS5B nonnucleoside polymerase inhibitors, and NS5A inhibitors (*Liang et al 2013*).
 - The first DAA-containing regimens were single-ingredient DAAs that needed to be used in combination with peginterferon (PegIFN)/ribavirin (RBV). However, several IFN-free combination products and regimens have been approved since 2014. Some of these regimens also remove the need for RBV in select populations.
- This review provides information on the DAAs, including: Daklinza, Epclusa, Harvoni, Mavyret, Sovaldi, Viekira Pak, Vosevi, and Zepatier.
 - In May 2018, AbbVie announced the discontinuation of Viekira XR (ombitasvir/paritaprevir/ritonavir and dasabuvir) and Technivie (ombitasvir/paritaprevir/ritonavir). These discontinuations were voluntary, and not due to any safety, efficacy, or quality issues. These products will no longer be available, effective January 1, 2019 (*FDA Drug Shortages 2018*).
- Medispan Class: Hepatitis C Agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Daklinza (daclatasvir)	--
Epclusa (sofosbuvir/velpatasvir)	--*
Harvoni (ledipasvir/sofosbuvir)	--*
Mavyret (glecaprevir/pibrentasvir)	--
Sovaldi (sofosbuvir)	--
Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)	--
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	--
Zepatier (elbasvir/grazoprevir)	--

*Generic anticipated to launch in January 2019

(Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Daklinza (daclatasvir)	Epclusa (sofosbuvir-velpatasvir)	Harvoni* (ledipasvir/sofosbuvir)	Mavyret (glecaprevir-pibrentasvir)	Sovaldi* (sofosbuvir)	Viekira Pak (ombitasvir/paritaprevir/ritonavir/dasabuvir)	Vosevi† (sofosbuvir-velpatasvir-voxilaprevir)	Zepatier (elbasvir/grazoprevir)
Genotype 1	✓	✓	✓	✓	✓	✓	✓	✓
Genotype 2		✓		✓	✓		✓	
Genotype 3	✓	✓		✓	✓		✓	
Genotype 4		✓	✓	✓	✓		✓	✓
Genotype 5		✓	✓	✓			✓	
Genotype 6		✓	✓	✓			✓	

* Harvoni and Sovaldi are the only agents approved in pediatric patients; Harvoni is indicated for the treatment of pediatric patients 12 years of age and older or weighing at least 35 kg with HCV genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis; Sovaldi is indicated for the treatment of chronic HCV genotype 2 or 3 infection in pediatric patients 12 years of age and older or weighing at least 35 kg without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.

† Only approved in patients with genotypes 1, 2, 3, 4, 5, or 6 with prior failure to an NS5A inhibitor-containing regimen or patients with genotypes 1a or 3 previously treated with a sofosbuvir-containing regimen without an NS5A inhibitor.

(Prescribing information: Daklinza 2017, Epclusa 2017, Harvoni 2017, Mavyret 2018, Sovaldi 2018, Viekira Pak 2018, Vosevi 2017, Zepatier 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Daklinza

- The clinical safety and efficacy of daclatasvir in combination with sofosbuvir and with or without RBV was evaluated in 3 pivotal phase 3 trials.
 - ALLY-1 was a multicenter (MC), open-label (OL) study in patients (genotype 1 to 6 included) with advanced cirrhosis (n = 60) or patients with HCV recurrence post-liver transplant (N = 53). Patients received daclatasvir plus sofosbuvir plus RBV for 12 weeks. In the advanced cirrhosis cohort, 82% of genotype 1 patients achieved SVR12 (SVR12 in overall cohort: 83%). In the post-transplant cohort, 95% of genotype 1 patients achieved SVR12 (SVR12 in overall cohort: 94%) (Poordad et al 2016).

- ALLY-2 was a MC, OL, randomized study (n = 153) in patients (genotype 1 to 6 included) with HCV/human immunodeficiency virus (HIV) co-infection. Among patients who received 12 weeks of daclatasvir plus sofosbuvir therapy, 96% and 97% of treatment-naïve HCV genotype 1 and treatment-experienced HCV genotype 1a patients achieved SVR12, respectively. All treatment-naïve and treatment-experienced patients with genotype 1b (23/23), genotype 2 (13/13), genotype 3 (10/10), or genotype 4 (3/3) infection achieved SVR12 (*Wyles et al 2015*).
- ALLY-3 was a MC, OL study in genotype 3 patients (n = 152), including those with compensated cirrhosis. Patients received daclatasvir plus sofosbuvir for 12 weeks. The SVR12 rates were 90% in treatment-naïve patients and 86% in treatment-experienced patients, with an overall SVR12 rate of 89%. SVR12 rates were higher in patients without cirrhosis (96%) than in patients with cirrhosis. In cirrhotic treatment-naïve and treatment-experienced patients, the SVR12 rate was 58% and 69%, respectively (*Nelson et al 2015*).
- ALLY-3C was a phase 3, OL, MC, single-arm study that examined the efficacy of daclatasvir plus sofosbuvir plus RBV for 24 weeks in patients (n = 78) with HCV genotype 3 and compensated cirrhosis. SVR12 was achieved in 87% of patients; SVR12 rates were 93% and 79% for treatment-naïve and treatment-experienced patients, respectively (*Poordad et al 2018*).
- ALLY-3+ was a phase 3, OL, MC study that compared 12 weeks (n = 24) vs 16 weeks (n = 26) of daclatasvir plus sofosbuvir plus RBV in patients with advanced fibrosis or cirrhosis. SVR12 was 88% in the 12-week treatment group and 92% in the 16-week group, giving an overall rate in all treated patients of 90%. All patients with advanced fibrosis achieved SVR12 (*Leroy et al 2016*).
- Several recent real world and observational studies have also found daclatasvir plus sofosbuvir, with or without RBV, to be highly effective and well tolerated for the treatment of genotype 1 or 3 infection (*Alonso et al 2016, Pol et al 2017, Welzel et al 2016*).

Epclusa

- The clinical safety and efficacy of Epclusa was evaluated in 4 pivotal phase 3 trials.
 - ASTRAL-1 was a double-blind (DB), placebo-controlled, MC, randomized trial in previously treated or untreated patients who were chronically infected with HCV genotype 1, 2, 4, 5, or 6. Overall, the rate of SVR among patients who received 12 weeks of Epclusa was 99% (618/624) (95% confidence interval [CI], 98 to > 99), which was significantly superior to the prespecified performance goal of 85% (p < 0.001). None of the 116 patients in the placebo group had an SVR (*Feld et al 2015*).
 - ASTRAL-2 was an OL, active-control (AC), MC, randomized trial comparing Epclusa for 12 weeks (n = 134) vs sofosbuvir plus RBV for 12 weeks (n = 132) in patients with genotype 2 infection. The rate of SVR12 was 99% (133/134) (95% CI, 96 to 100) among those who had received Epclusa as compared with 94% (124/132) (95% CI, 88 to 97) among those who had received sofosbuvir plus RBV (*Foster et al 2015*).
 - ASTRAL-3 was an OL, AC, MC, randomized trial comparing Epclusa for 12 weeks (n = 277) vs sofosbuvir plus RBV for 24 weeks (n = 275) in patients with genotype 3 infection. The rate of SVR12 was 95% (95% CI, 92 to 98) among those who had received Epclusa, as compared with 80% (95% CI, 75 to 85) among those who had received sofosbuvir plus RBV. The overall SVR rate with Epclusa was significantly superior to that with sofosbuvir plus RBV. The strata-adjusted absolute difference was 14.8% (95% CI, 9.6 to 20.0, p < 0.001) (*Foster et al 2015*).
 - ASTRAL-4 was an OL, MC, randomized trial comparing Epclusa with or without RBV for 12 weeks or Epclusa for 24 weeks in patients infected with HCV genotypes 1 through 6 and with decompensated cirrhosis. Rates of SVR12 were 83% (95% CI, 74 to 90) in patients who received Epclusa for 12 weeks, 94% (95% CI, 87 to 98) among those who received Epclusa plus RBV for 12 weeks, and 86% (95% CI, 77 to 92) among those who received Epclusa for 24 weeks. Post-hoc analyses did not detect any significant differences in rates of SVR among the 3 treatment groups (*Curry et al 2015*).
- A randomized, OL trial conducted in Spain compared 12 weeks of Epclusa to 12 weeks of Epclusa plus RBV in patients (n = 204) with HCV genotype 3 and compensated cirrhosis. SVR12 rates were 91% and 96% in the Epclusa and Epclusa plus RBV groups, respectively (*Esteban et al 2018*).
- A meta-analysis of 6 randomized controlled trials (n = 1427) found that 12 weeks of Epclusa treatment resulted in SVR12 rates of 98.2%, 99.4%, 94.7%, 99.6%, 97.1%, and 98.8% in HCV genotypes 1, 2, 3, 4, 5, and 6, respectively (*Ahmed H et al 2018[a]*).

Harvoni

Adults

- The efficacy and safety of Harvoni were evaluated in 4 trials in genotype 1 HCV monoinfected patients, 1 trial in genotype 1 or 4 HCV/HIV-1 co-infected patients, 3 trials in genotype 4, 5, or 6 HCV monoinfected patients and 2 trials in genotype 1 or 4 HCV infected pre-transplant patients with decompensated cirrhosis (Child-Pugh B and C) or post-liver transplant.
 - ION-1 was a randomized, OL trial in treatment-naïve patients (n = 865) with genotype 1 HCV with or without cirrhosis. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. In the trial, SVR12 rates of 97 to 99% were achieved (*Afdhal et al 2014[a]*).
 - ION-2 was a randomized, OL trial in patients (n = 440) with genotype 1 HCV with or without cirrhosis who failed prior therapy with an IFN-based regimen, with or without a protease inhibitor. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. SVR12 rates of up to 99% were achieved (*Afdhal et al 2014[b]*).
 - ION-3 was a randomized, OL trial in treatment-naïve patients (n = 647) with non-cirrhotic HCV genotype 1 infection. Patients randomized to treatment with Harvoni for 8 or 12 weeks or Harvoni plus RBV for 8 weeks demonstrated SVR12 rates of 93 to 95% (*Kowdley et al 2014*).
 - ION-4 was an OL, MC trial in 335 patients evaluating 12 weeks of Harvoni in treatment-naïve and treatment-experienced cirrhotic or non-cirrhotic HIV/HCV co-infected patients. SVR12 rates were high overall (96%) with comparable rates to the HCV monoinfected population (*Naggie et al 2015*).
 - SIRIUS was a DB, MC, French study in which patients with cirrhosis who did not respond to PegIFN and RBV plus telaprevir or boceprevir, were randomized to placebo for 12 weeks followed by Harvoni plus RBV for 12 weeks (n = 77) or Harvoni plus placebo for 24 weeks (n = 78). The overall SVR12 rates were 96% and 97% for Harvoni plus RBV for 12 weeks and Harvoni plus placebo for 24 weeks, respectively (*Bourlière et al 2015*).
 - Study 1119 was an OL study evaluating Harvoni for 12 weeks in patients with genotype 4 (n = 44) or 5 infection (n = 41), with or without compensated cirrhosis. The study was conducted at 5 sites in France. There were high SVR12 rates (≥ 89%) with 12 weeks of Harvoni in all patient subgroups and similar rates for genotype 4 vs genotype 5 infection (*Abergel et al 2016*).
 - In an OL, randomized study, Harvoni for 12 weeks was compared to sofosbuvir plus RBV for 24 weeks in a cohort of Egyptian patients (n = 200) with treatment-naïve genotype 4 HCV. SVR12 was higher with Harvoni (99% vs 80% with sofosbuvir plus RBV) (*Ahmed OA et al 2018*). Another OL randomized study in Egyptian patients (n = 255) compared Harvoni and Harvoni plus RBV for 8 or 12 weeks. SVR12 rates were 95% and 90% among patients receiving 8 weeks of Harvoni and Harvoni plus RBV, respectively. The SVR12 rate for patients receiving 12 weeks of Harvoni (with or without RBV) was 98% (*Shiha et al 2018*).
 - ELECTRON-2 was an OL trial that enrolled patients from 2 centers in New Zealand. The trial evaluated Harvoni for 12 weeks in patients with genotype 6 infection (n = 25). The rate of SVR12 was 96%. The single patient who did not reach SVR12 was a patient who withdrew consent during week 8 of treatment and therefore did not receive the full course of treatment (*Gane et al 2015*).
 - SOLAR-1 and SOLAR-2 were OL, MC trials that evaluated 12 and 24 weeks of treatment with Harvoni in combination with RBV in patients with genotype 1 and 4 infection who had undergone liver transplantation and/or who had decompensated liver disease. The 2 trials were identical in study design. The SVR12 rates observed with 24 weeks of Harvoni plus RBV were similar to the SVR12 rates observed with 12 weeks of treatment. In pre-transplant patients with decompensated cirrhosis, the SVR12 rate for Harvoni plus RBV for 12 weeks was 87% (80/92). In post-transplant patients (with or without cirrhosis), the SVR12 was 93% (194/208) (*Charlton et al 2015; Manns et al 2016*).

Pediatric

- A phase 2, OL, MC study (N = 100) evaluated Harvoni for 12 weeks in patients aged 12 to 17 years with chronic HCV genotype 1 infection. Overall, 98% of patients reached SVR12. No patient had virologic failure; 2 patients who did not achieve SVR12 were lost to follow-up either during or after treatment (*Balistreri et al 2016*).

Mavyret

- The efficacy of Mavyret in patients who were treatment-naïve or treatment-experienced to combinations of PegIFN, RBV and/or sofosbuvir (PRS) with genotype 1, 2, 4, 5, or 6 infection without cirrhosis was studied in 5 trials using 8- or 12-week durations: ENDURANCE-1, ENDURANCE-2, ENDURANCE-4, SURVEYOR-1 (Part 2), and SURVEYOR-2 (Part 2 and Part 4).
 - ENDURANCE-1 was a randomized, MC, OL trial comparing the efficacy of 8 and 12 weeks of treatment with Mavyret in patients with genotype 1 infection with or without HIV-1 co-infection. The SVR rate was 99% (348/351) and 99.7%

- (351/352) in the Mavyret 8- and 12-week arms, respectively (*Mavyret prescribing information 2018*, Zeuzem et al 2018).
- ENDURANCE-4, SURVEYOR-1, and SURVEYOR-2 were OL, MC trials evaluating the safety and efficacy of Mavyret in treatment-naïve or PRS treatment-experienced patients. ENDURANCE-4 and SURVEYOR-1 evaluated 12 weeks of Mavyret in patients with genotypes 5 and 6. The overall SVR rate was 100% (57/57). SURVEYOR-2 evaluated 8 weeks of Mavyret in patients with genotypes 2, 4, 5, or 6; the SVR rate was 98% (193/197), 93% (43/46), 100% (2/2), and 100% (10/10), respectively (*Asselah et al 2017*, *Asselah et al 2018[a]*, *Mavyret prescribing information 2018*).
 - ENDURANCE-2 was a randomized, DB, placebo-controlled, MC study assessing the efficacy of Mavyret for 12 weeks in non-cirrhotic patients with genotype 2 HCV (n = 196). The SVR12 rate in the treatment group was 99% (*Asselah et al 2018[a]*).
 - The efficacy of Mavyret in patients who were treatment-naïve or PRS treatment-experienced with genotype 1, 2, 4, 5, or 6 with compensated cirrhosis was studied in the OL, single-arm EXPEDITION-1 trial. Patients were treated with 12 weeks of Mavyret. The overall SVR rate was 99% (145/146) (*Forns et al 2017*).
 - The efficacy of Mavyret in patients without cirrhosis or with compensated cirrhosis who were treatment-naïve or PRS treatment-experienced with genotype 3 infection was studied in ENDURANCE-3 and in SURVEYOR-2 (Part 3).
 - ENDURANCE-3 was a randomized, OL, AC trial in treatment-naïve patients. Patients were randomized (2:1) to either Mavyret for 12 weeks or to the combination of Sovaldi and Daklinza for 12 weeks; subsequently the trial included a third non-randomized arm with Mavyret for 8 weeks. The SVR rate for 8 weeks of Mavyret, 12 weeks of Mavyret, and 12 weeks of Sovaldi plus Daklinza was 94.9% (149/157), 95.3% (222/233), and 96.5% (111/115), respectively. The treatment difference for 12 weeks of Mavyret vs 12 weeks of sofosbuvir plus daclatasvir was -1.2% (95% CI, -5.6% to 3.1%). The treatment difference for 8 weeks vs 12 weeks of Mavyret was -0.4% (95% CI, -5.4% to 4.6%) (*Mavyret prescribing information 2018*, *Zeuzem et al 2018*).
 - SURVEYOR-2 (Part 3) was an OL trial randomizing PRS treatment-experienced patients with genotype 3 infection without cirrhosis to 12 or 16 weeks of treatment. In addition, the trial evaluated the efficacy of Mavyret in genotype 3 infected patients with compensated cirrhosis in 2 dedicated treatment arms using 12-week (treatment-naïve only) and 16-week (PRS treatment-experienced only) durations. The SVR rate was 98% (39/40) in treatment-naïve patients with cirrhosis who were treated with 12 weeks of Mavyret. The SVR rate was 96% (66/69) in PRS treatment-experienced patients, with or without cirrhosis, who were treated with 16 weeks of Mavyret (*Mavyret prescribing information 2018*, *Wyles et al 2017*).
 - A pooled analysis of 5 trials in patients (n = 693) with HCV genotype 3 found that treatment with Mavyret for 8 or 12 weeks achieved SVR12 in 95% of treatment-naïve patients without cirrhosis; treatment-naïve patients with cirrhosis who were treated for 12 weeks had an SVR12 rate of 97%. Treatment-experienced patients without cirrhosis achieved SVR12 rates of 90% and 96% with 12 and 16 weeks of Mavyret treatment, respectively. Treatment-experienced patients with cirrhosis achieved SVR12 rates of 94% with 16 weeks of Mavyret treatment (*Flamm et al 2018*).
 - ENDURANCE-5,6 was a single-arm, OL, MC trial examining the efficacy of Mavyret in patients (n = 84) with HCV genotypes 5 and 6. Patients without cirrhosis or with compensated cirrhosis were treated with 8 or 12 weeks of Mavyret, respectively. The overall SVR12 rate was 97.6%, with 95.7% and 98.4% of patients with HCV genotype 5 and 6 infections, respectively, achieving SVR12 (*Asselah et al 2018[b]*).
 - EXPEDITION-2 was an OL study in HCV/HIV-1 co-infected patients (n = 153) evaluating Mavyret in HCV genotypes 1 through 6 with or without compensated cirrhosis for 8 or 12 weeks, respectively. Treatment-naïve and treatment-experienced patients were both included. The overall SVR12 rate was 98% (*Rockstroh et al 2018*).
 - EXPEDITION-4 was an OL, single-arm, MC trial evaluating the safety and efficacy in patients with severe renal impairment (chronic kidney disease [CKD] Stages 4 and 5; 82% were on hemodialysis) with compensated liver disease (with and without cirrhosis). The study included patients with (19%) or without compensated cirrhosis (81%). The SVR rate was 98% (102/104). Of the 2 patients who failed, 1 discontinued the medication and the other was lost to follow-up (*Gane et al 2017*, *Mavyret prescribing information 2018*).
 - MAGELLAN-1 was a randomized, OL trial in genotype 1- or 4-infected patients who failed a previous regimen containing an NS5A inhibitor and/or NS3/4A protease inhibitor. Due to higher rates of virologic failure and treatment-emergent drug resistance, the data did not support labeling for treatment of HCV genotype 1-infected patients who are both NS3/4A protease inhibitor and NS5A inhibitor-experienced (*Mavyret prescribing information 2018*, *Poordad et al 2017*).

- In protease inhibitor-experienced patients (but NS5A inhibitor-naïve), the SVR rate was 92% (23/25) for patients treated with Mavyret for 12 weeks. In NS5A-experienced patients (but protease inhibitor-naïve), the SVR rate was 94% (16/17).
- MAGELLAN-2 was an OL trial that included treatment-naïve or treatment-experienced patients (n = 100) with chronic HCV genotype 1 through 6 who had received a liver or kidney transplant. The overall SVR12 was 98% after 12 weeks of therapy (Reau et al 2018). In 2018, Mavyret received approval for use in liver and kidney transplant recipients (Mavyret prescribing information 2018).
- In a pooled analysis of 9 trials in patients (n = 2041) with HCV genotypes 1 through 6 without cirrhosis, treatment with Mavyret for 8 or 12 weeks resulted in SVR12 rates of 98% and 99%, respectively (Puoti et al 2018).

Sovaldi

Adults

- The clinical safety and efficacy of sofosbuvir were evaluated in 6 pivotal phase 3 trials.
 - NEUTRINO was a single-arm, OL study of sofosbuvir in combination with IFN and RBV in patients infected with HCV genotype 1, 4, 5, or 6. SVR was achieved in 90% of patients at 12 weeks (Lawitz et al 2013).
 - FISSION was a randomized, OL, AC, non-inferiority study in patients with HCV genotype 2 or 3. Patients received treatment with sofosbuvir plus RBV for 12 weeks or PegIFN plus RBV for 24 weeks. An SVR was reported in 67% of patients in both treatment groups at 12 weeks after the end of treatment (Lawitz et al 2013).
 - In POSITRON, HCV genotype 2 or 3 patients who had previously discontinued IFN therapy due to adverse events, who had a concurrent medical condition precluding therapy with an IFN, or who decided against treatment with an IFN-containing regimen were randomized to receive treatment with sofosbuvir and RBV or matching placebos. Rates of SVR at 12 weeks were significantly higher in the sofosbuvir treatment group compared to placebo (78 vs 0%, respectively; p < 0.001) (Jacobson et al 2013).
 - In FUSION, patients who did not achieve SVR with prior IFN therapy (relapsers or nonresponders) were randomized to receive treatment with sofosbuvir and RBV for 12 or 16 weeks. Rates of SVR were 50% with 12 weeks of treatment, as compared with 73% with 16 weeks of treatment (Jacobson et al 2013).
 - The VALENCE trial evaluated sofosbuvir in combination with RBV for the treatment of genotype 2 or 3 HCV infection in treatment-naïve patients or patients who did not achieve SVR with prior IFN-based treatment, including those with compensated cirrhosis. Rates of SVR were 93% in genotype 2 patients and 84% in genotype 3 patients (Zeuzem et al 2014[a]).
 - PHOTON-1 was an OL trial evaluating treatment with 12 or 24 weeks of sofosbuvir in combination with RBV in genotype 1, 2, or 3 CHC patients co-infected with HIV-1. Genotype 2 and 3 patients were either treatment-naïve or experienced, whereas genotype 1 patients were treatment-naïve. Rates of SVR were similar to those observed in patients with HCV mono-infection across all genotypes (Sulkowski et al 2014).

Pediatric

- Study 1112 was an OL trial evaluating treatment with Sovaldi in combination with RBV in pediatric patients 12 years of age and older with genotype 2 or 3 HCV infection. Patients with HCV genotype 2 or 3 infection in the trial were treated with Sovaldi and weight-based RBV for 12 or 24 weeks, respectively. The majority of patients were treatment-naïve (83%), and 73% were infected by vertical transmission; 40% were assessed as not having cirrhosis (the remainder did not have a cirrhosis determination). SVR12 rates were 100% (13/13) for patients with genotype 2 and 97% (38/39) for genotype 3. The single patient who did not achieve SVR was lost to follow-up after achieving SVR4 (Wirth et al 2017).

Vosevi

- The efficacy of Vosevi was evaluated in 2 pivotal trials in DAA-experienced patients.
 - POLARIS-1 was a randomized, DB, PC trial that evaluated 12 weeks of treatment with Vosevi compared with 12 weeks of placebo in DAA-experienced patients with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis who previously failed a regimen containing an NS5A inhibitor. Overall, 51% of patients had been previously treated with ledipasvir (the NS5A component of Harvoni). The remaining patients were treated with other NS5A inhibitors. The overall SVR rate was 96% (253/263). The SVR rate was 99% (140/142) and 93% (113/121) in patients without cirrhosis and with cirrhosis, respectively (Bourlière et al 2017).
 - POLARIS-4 was a randomized, OL trial that evaluated 12 weeks of treatment with Vosevi and 12 weeks of treatment with Eplclusa in patients with genotype 1, 2, 3, or 4 HCV infection without cirrhosis or with compensated cirrhosis who

had previously failed an HCV DAA-containing regimen that did not include an NS5A inhibitor. In the trial, prior DAA regimens contained sofosbuvir (85%) with the following: PegIFN and RBV or just RBV (69%), HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir; 15%) and investigational DAA (< 1%). The SVR12 rate was 98% (178/182) (95% CI, 95 to 99; significantly superior to the prespecified performance goal of 85% [$p < 0.001$]) for patients receiving Vosevi for 12 weeks. The SVR12 rate was 90% (136/151) (95% CI, 84 to 94, not significantly superior to the prespecified performance goal of 85% [$p = 0.09$]) for patients receiving Epclusa for 12 weeks. One patient had viral breakthrough and 14 patients relapsed (*Bourlière et al 2017*).

Viekira Pak

- Efficacy and safety of Viekira Pak were evaluated in 8 pivotal clinical trials with chronic HCV genotype 1 infection:
 - Treatment-naïve genotype 1a and 1b (SAPPHIRE-I)
 - Treatment-experienced genotype 1a and 1b (SAPPHIRE-II)
 - Treatment-experienced genotype 1b (PEARL-II)
 - Treatment-naïve genotype 1b (PEARL-III)
 - Treatment-naïve genotype 1a (PEARL-IV)
 - Treatment-naïve and -experienced genotype 1a and 1b with cirrhosis (TURQUOISE-II)
 - Treatment-naïve and -experienced genotype 1b with cirrhosis (TURQUOISE-III).
 - Treatment-naïve and -experienced genotype 1b with cirrhosis (TURQUOISE-IV)
- SAPPHIRE-I and SAPPHIRE-II were MC, randomized, DB, PC trials. Patients were randomized to Viekira Pak plus RBV for 12 weeks or placebo. Patients in the placebo treatment arm received placebo for 12 weeks, after which they received OL Viekira Pak plus RBV for 12 weeks (*Feld et al 2014, Zeuzem et al 2014[b]*).
 - In SAPPHIRE-I ($n = 631$), SVR12 was achieved in 96.2% (95% CI, 94.5 to 97.9) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate with telaprevir plus PegIFN/RBV.
 - In SAPPHIRE-II ($n = 394$), SVR12 was achieved in 96.3% (95% CI, 94.2 to 98.4) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate among patients who had previously been treated with PegIFN/RBV and who received retreatment with telaprevir plus PegIFN/RBV.
- In PEARL-II ($n = 186$), patients without cirrhosis were randomized to receive OL Viekira Pak with or without RBV for 12 weeks of treatment (*Andreone et al 2014*).
 - Rates of SVR12 were 96.6% (95% CI, 92.8 to 100) with Viekira Pak plus RBV and 100% (95% CI, 95.9 to 100) with Viekira Pak alone. Rates of SVR in both treatment groups were non-inferior and superior to the historical rate for telaprevir plus PegIFN/RBV in comparable treatment-experienced patients.
 - Non-inferiority of treatment with Viekira Pak alone compared to Viekira Pak plus RBV was met (treatment difference in SVR12 rates, 3.4% [95% CI, -0.4 to 7.2]).
- PEARL-III and PEARL-IV were MC, DB, placebo controlled trials. Patients without cirrhosis were randomized to receive Viekira Pak with or without RBV for 12 weeks of treatment (*Ferenci et al 2014*).
 - In PEARL-III ($n = 419$), treatment with Viekira Pak resulted in SVR12 rates of 99.5% (95% CI, 98.6 to 100) with RBV and 99% (95% CI, 97.7 to 100) without RBV in patients with genotype 1b infection.
 - In PEARL-IV ($n = 305$), treatment with Viekira Pak resulted in SVR12 rates of 97% (95% CI, 93.7 to 100) with RBV and 90.2% (95% CI, 86.2 to 94.3) without RBV in patients with genotype 1a infection.
- The OL TURQUOISE-II trial ($n = 380$) enrolled patients with compensated cirrhosis (Child-Pugh A) or liver scarring with few to no outward symptoms who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak in combination with RBV for 12 or 24 weeks of treatment. Patients who previously failed therapy with a treatment regimen that included a DAA were excluded (*Poordad et al 2014*).
 - Patients who received 12 weeks of treatment had an SVR12 response of 91.8% (97.5% CI, 87.6 to 96.1).
 - Those patients who received 24 weeks of treatment achieved an SVR12 rate of 95.9% (97.5% CI, 92.6 to 99.3).
 - Rates of SVR12 in the 12- and 24-week treatment groups were non-inferior and superior to the historical rate with telaprevir plus PegIFN/RBV among patients with HCV genotype 1 infection and cirrhosis. The difference in the rates of SVR between the 2 treatment groups was not significant.
- The OL TURQUOISE-III trial ($n = 60$) enrolled genotype 1b patients with compensated cirrhosis who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak for 12 weeks. SVR12 was achieved in all patients enrolled in the study (*Feld et al 2016*).
- The OL TURQUOISE-IV trial ($n = 36$) enrolled genotype 1b patients in Russia and Belarus with compensated cirrhosis who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients received Viekira Pak plus RBV for 12 weeks. SVR12 was achieved in all patients enrolled in the study (*Isakov et al 2018*).

- Safety and efficacy of Viekira Pak were also evaluated in liver transplant patients and in patients with HCV genotype 1 co-infected with HIV-1.
 - CORAL-I was a phase 2, OL trial in HCV genotype 1 liver transplant recipients who were at least 12 months post transplantation with mild fibrosis (Metavir score < F2). Patients received treatment with Viekira Pak with RBV for 24 weeks. Of the 34 patients enrolled, 33 achieved an SVR12, for a rate of 97% (95% CI, 85 to 100) (*Kwo et al 2014*).
 - TURQUOISE-I was a phase 3, randomized, OL trial in 63 patients with treatment-naïve or -experienced HCV genotype 1 infection who were co-infected with HIV-1. Patients on a stable antiretroviral therapy regimen were treated for 12 or 24 weeks with Viekira Pak in combination with RBV. SVR12 rates were 91% for patients with HCV genotype 1a infection and 100% for those with genotype 1b infection (*Wyles et al 2014*).

Zepatier

- The safety and efficacy of Zepatier were evaluated in 7 pivotal clinical trials including patients with genotype 1 or 4 infection. A small number of patients with other HCV genotypes were also included in the clinical trials; however, Zepatier is only indicated for genotypes 1 and 4.
 - C-EDGE TN was a DB, PC, MC, randomized study in treatment-naïve patients with genotype 1, 4, or 6 infection. Of the 316 patients receiving Zepatier for 12 weeks, 95% (95% CI, 92 to 97) achieved SVR12. SVR12 was achieved in 97% (95% CI, 90 to 100) of cirrhotic patients and 94% (95% CI, 90 to 97) of noncirrhotic patients (*Zeuzem et al 2015*).
 - C-EDGE CO-INFECTION was an OL, MC trial in treatment-naïve patients with genotype 1, genotype 4, and genotype 6 infection who were co-infected with HIV. All patients (n = 218) received Zepatier for 12 weeks. In the overall population, 96% achieved SVR12 (95% CI, 92.9 to 98.4), exceeding the historical reference rate of 70% (*Rockstroh et al 2015*).
 - C-SURFER was a DB, placebo-controlled, MC, randomized study, evaluating Zepatier for 12 weeks in patients with genotype 1 infection with CKD stage 4 to 5. Of the 122 patients receiving Zepatier, 6 were excluded from the modified full analysis set population for reasons other than virologic failure. Of the 116 remaining patients, 115 achieved SVR12, a rate better than the historical control rate of 45% (p < 0.001) (*Roth et al 2015*).
 - C-SCAPE was an OL, randomized study that evaluated the efficacy of Zepatier for 12 weeks, with or without RBV, in patients with genotype 4, 5, or 6 infection. In patients with genotype 4 infection, SVR12 was achieved in 100% (10/10) of patients receiving Zepatier with RBV vs 90% (9/10) in patients receiving Zepatier alone (*Brown et al 2015, Brown et al 2018*).
 - C-EDGE TE was an OL, MC, randomized study evaluating 12 or 16 weeks of Zepatier, with or without RBV in patients with genotype 1, 4, or 6 HCV infection and previous treatment with Peg IFN/RBV. SVR12 was achieved in 92.4% (97/105) receiving Zepatier alone for 12 weeks, 94.2% (98/104) receiving Zepatier plus RBV for 12 weeks, 92.4% (97/105) receiving Zepatier alone for 16 weeks, and 97.2% (103/106) receiving Zepatier plus RBV (*Kwo et al 2017*).
 - C-SALVAGE was an OL, MC study evaluating Zepatier plus RBV for 12 weeks in patients (n = 79) with genotype 1 infection who failed a regimen containing PegIFN/RBV and another DAA. SVR12 was achieved in 96% (95% CI, 89.3 to 99.2) of patients. The 3 patients not achieving SVR12 had a past history of virologic failure (*Forns et al 2015*).
 - C-CORAL was a randomized, DB, placebo-controlled study evaluating Zepatier for 12 weeks in treatment-naïve patients (n = 489) with genotype 1, 4, or 6 HCV infection. SVR12 was achieved in 94.4% of patients receiving Zepatier. SVR12 rates of 98.2%, 91.9%, and 66.7% were seen in patients with genotype 1b, 1a, and 6 infections, respectively (*Wei et al 2018*).
- A meta-analysis of 8 trials (n = 1297) found an overall SVR rate of 96.6% with Zepatier treatment in patients with genotype 1 HCV (*Ahmed H et al 2018[b]*).
- In a pooled analysis of clinical trial data, treatment-naïve and treatment-experienced patients with genotype 4 HCV infection (n = 155) had SVR12 rates of 96.4% (treatment-naïve) and 88.6% (treatment-experienced) after 12 or 16 weeks of Zepatier with or without RBV (*Asselah et al 2018[c]*).

CLINICAL GUIDELINES

- In order to provide healthcare professionals with timely guidance, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management (*AASLD-IDSA 2018*).

- Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and duration.
- The guidance also lists alternative regimens, which are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. For a listing of alternative regimens, refer to the web-based guidance for full details.
- For the general genotype 1 population, the guidance recommends 4 different regimens considered to have comparable efficacy: Epclusa, Harvoni, Mavyret, and Zepatier. The level of evidence and treatment duration depend on the genotype 1 subtype, prior treatment status (naïve or experienced), and the presence of cirrhosis.
- The guidance recommends Epclusa and Mavyret for patients with genotype 2 or 3 infection.
- The guidance recommends Epclusa, Harvoni, Mavyret, and Zepatier for the treatment of genotype 4 infection. The guidance recommends Epclusa, Harvoni, and Mavyret for treatment of genotype 5 and 6.
- The guidance provides recommendations for several unique patient populations, including patients who have failed prior therapy with DAAs, co-infection with HIV/HCV, decompensated cirrhosis, recurrent HCV infection in the post-transplant setting, or renal impairment. Some key recommendations include:
 - Epclusa, Harvoni (listed as an alternative for patients with compensated cirrhosis), and Mavyret are recommended for genotype 1 patients with prior failure to HCV NS3/4A protease inhibitors. Epclusa (genotype 1b), Mavyret (regardless of genotype 1 subtype), and Vosevi (genotype 1a) are recommended for patients with prior failure to sofosbuvir-containing regimens.
 - Vosevi is recommended in genotype 1, 3, 4, 5, or 6 patients with prior failure to an NS5A inhibitor-containing regimen.
 - Sovaldi-based regimens (ie, Epclusa, Harvoni, Sovaldi plus Daklinza) are recommended for patients with decompensated cirrhosis.
 - HIV/HCV-co-infected patients should be treated and re-treated the same as patients without HIV infection, after recognizing and managing interactions with antiretroviral medications.
 - For patients with stage 4 or 5 CKD (creatinine clearance below 30 mL/min), Mavyret (regardless of genotype) and Zepatier (genotypes 1 and 4 only) are recommended. For kidney transplant recipients, Harvoni (genotypes 1 and 4 only) and Mavyret are recommended.

SAFETY SUMMARY

- Due to the DAAs used in combination therapy with PegIFN and RBV, all contraindications to those 2 medications (PegIFN and RBV) also apply to the class. This includes a contraindication for use in pregnancy due to the RBV component.
- Mavyret is contraindicated in patients with severe hepatic impairment (Child-Pugh C) and coadministration with atazanavir and rifampin.
- Viekira Pak is contraindicated in patients with:
 - Moderate to severe hepatic impairment (Child-Pugh B and C) due to the risk of potential toxicity.
 - Known hypersensitivity to ritonavir (eg, toxic epidermal necrolysis or Stevens-Johnson syndrome).
 - Concomitant use of drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
 - Concomitant use of drugs that are moderate or strong inducers of CYP3A.
 - Concomitant use of drugs that are strong inducers or strong inhibitors of CYP2C8
- Vosevi is contraindicated in patients with rifampin coadministration.
- Zepatier is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). It is also contraindicated with organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors, strong inducers of CYP3A, and efavirenz.
- Daklinza is contraindicated in combination with drugs that strongly induce CYP3A.
- Key warnings and precautions for the DAAs include:
 - Serious symptomatic bradycardia may occur in patients taking amiodarone and sofosbuvir in combination with another DAA (eg, Sovaldi plus Daklinza, Epclusa, Harvoni, Vosevi).
 - Viekira Pak carries a risk of hepatic decompensation and hepatic failure in patients with cirrhosis.
- Overall, DAA combination therapies are well tolerated and discontinuations due to adverse events are not common.
 - The most common adverse reactions observed with each treatment regimen listed below include:
 - Daklinza in combination with Sovaldi: headache and fatigue
 - Daklinza in combination with Sovaldi and RBV: headache, anemia, fatigue, and nausea

- Eplclusa: headache and fatigue
 - Eplclusa and RBV in patients with decompensated cirrhosis: fatigue, anemia, nausea, headache, insomnia, and diarrhea
 - Harvoni: fatigue, headache, and asthenia
 - Mavyret: headache and fatigue
 - Sovaldi in combination with RBV: fatigue and headache
 - Sovaldi in combination with PegIFN alfa and RBV: fatigue, headache, nausea, insomnia, and anemia
 - Viekira Pak with RBV: fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia.
 - Viekira Pak without RBV: nausea, pruritus, and insomnia
 - Vosevi: headache, fatigue, diarrhea, and nausea
 - Zepatier: fatigue, headache, and nausea.
 - Zepatier with RBV: anemia and headache
- In October 2016, the FDA announced that a new *Boxed Warning* would be added to all DAAs for HCV infection, regarding the risk of hepatitis B virus (HBV) reactivation. This *Boxed Warning* was based on case reports submitted to the FDA and from the published literature of HCV/HBV co-infected patients treated with DAAs from November 2013 to July 2016 (*FDA 2016*).
 - HBV can become reactivated in any patient who has a current or previous infection with HBV and is treated with direct-acting antivirals. In a few cases, HBV reactivation in patients treated with direct-acting antivirals resulted in serious liver problems or death.
 - The *Boxed Warning* was added to the labeling for all of the DAAs in February 2017. The warning directs healthcare providers to test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. HCV/HBV co-infected patients should be monitored for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Appropriate patient management for HBV infection should be initiated as clinically indicated.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Daklinza (daclatasvir)	Oral	One tablet once daily (60 mg dose); must be used in combination with Sovaldi	<p><i>Recommended dosage modification with CYP3A inhibitors and inducers:</i></p> <ul style="list-style-type: none"> • Strong CYP3A inhibitors and certain HIV antiviral agents: 30 mg once daily • Moderate CYP3A inducers and nevirapine: 90 mg once daily <p><i>Duration of therapy:</i></p> <ul style="list-style-type: none"> • 12 to 24 weeks (when used in combination with Sovaldi)
Eplclusa (sofosbuvir/velpatasvir)	Oral	One tablet once daily	<ul style="list-style-type: none"> • No dosage recommendation can be given for patients with severe renal impairment or end-stage renal disease (ESRD). <p><i>Duration of therapy:</i></p> <ul style="list-style-type: none"> • 12 weeks
Harvoni (ledipasvir/sofosbuvir)	Oral	One tablet once daily	<ul style="list-style-type: none"> • No dosage recommendation can be given for patients with severe renal impairment or ESRD.

Drug	Route	Usual Recommended Frequency	Comments
			<i>Duration of therapy:</i> <ul style="list-style-type: none"> 12 to 24 weeks
Mavyret (glecaprevir/pibrentasvir)	Oral	Three tablets daily	<ul style="list-style-type: none"> Contraindicated in patients with severe hepatic impairment (Child-Pugh C). Not recommended in patients with moderate hepatic impairment (Child-Pugh B). <i>Duration of therapy:</i> <ul style="list-style-type: none"> 8 to 16 weeks
Sovaldi (sofosbuvir)	Oral	One tablet once daily; must be used in combination with RBV ± PegIFN or Daklinza	<ul style="list-style-type: none"> Safety and efficacy have not been established in patients with severe renal impairment. <i>Duration of therapy:</i> <ul style="list-style-type: none"> 12 to 24 weeks (when used in combination with Daklinza)
Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)	Oral	Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening)	<ul style="list-style-type: none"> Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). <i>Duration of therapy:</i> <ul style="list-style-type: none"> 12 to 24 weeks
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	Oral	One tablet once daily	<ul style="list-style-type: none"> No dosage recommendation can be given for patients with severe renal impairment or ESRD. Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C). <i>Duration of therapy:</i> <ul style="list-style-type: none"> 12 weeks
Zepatier (elbasvir/grazoprevir)	Oral	One tablet once daily	<ul style="list-style-type: none"> Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with Zepatier to determine dosage regimen and duration. Contraindicated in patients with moderate hepatic impairment (Child-Pugh B) due to the lack of clinical safety and efficacy experience in HCV-infected Child-Pugh B patients, and in patients with severe hepatic impairment (Child-Pugh C) due

Drug	Route	Usual Recommended Frequency	Comments
			to a 12-fold increase in grazoprevir exposure. <i>Duration of therapy:</i> <ul style="list-style-type: none"> • 12 to 16 weeks

See the current prescribing information for full details

CONCLUSION

- Hepatitis C is a disease affecting primarily the liver that results from infection with the hepatitis C virus. Long-term complications include cirrhosis and hepatocellular carcinoma. Hepatitis C is the leading indication for liver transplant.
- Success at obtaining an SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications.
- PegIFN-free, DAA combination regimens, such as Epclusa, Harvoni, Mavyret, and Zepatier have become the standard of care for the treatment of genotype 1 infection. There is a lack of head-to-head trial data available comparing these regimens, but they are considered to have comparable efficacy and safety for treating the general genotype 1 population (AASLD-IDSA 2018).
- The only DAA fixed-dose combination products approved and recommended for the treatment of genotypes 2 and 3 infection are Mavyret and Epclusa (AASLD-IDSA 2018).
- Similar to genotype 1, several DAA combination regimens have demonstrated high SVR rates for genotype 4 infection. Epclusa, Harvoni, Mavyret, and Zepatier are recommended by the AASLD-IDSA guidance (AASLD-IDSA 2018).
- Data are limited for treatment of genotype 5 and 6 infection; however, Epclusa, Harvoni, and Mavyret are approved by the FDA and supported by the AASLD-IDSA guidance (AASLD-IDSA 2018).
- Of the combination products, Epclusa and Harvoni are the preferred treatment options in patients with decompensated cirrhosis (Child-Pugh B and C). Mavyret and Zepatier are recommended for patients with advanced kidney disease.

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Publication Date: 12/24/18