Formulary Drug Reviews

Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir

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Generic Name:	Ombitasvir/paritaprevir/ritonavir and dasabuvir
Proprietary Name:	Viekira Pak (AbbVie Inc)
Approval Rating:	4P (new combination and priority review)
Therapeutic Class:	CYP3A inhibitors, Hepatitis C Virus polymerase inhibitors, NS3/4A inhibitors, NS5A inhibitors
Similar Drugs:	Boceprevir, ledipasvir, sofosbuvir, simeprevir
Sound- and Look-Alike Names:	Vetira (non-US international name), Victrelis

INDICATIONS

Viekira Pak (ombitasvir [ABT-267]/paritaprevir [ABT-450]/ritonavir fixed-dose combination tablets copackaged with dasabuvir [ABT-333] tablets) is

approved with or without ribavirin for the treatment of patients with hepatitis C virus (HCV) genotype 1, including patients with compensated cirrhosis.¹ The drug combination is not recommended for use in patients with decompensated liver disease.¹ See **Table 1** for a comparison of the approved uses of various direct-acting antiviral agents for the treatment of HCV infections.¹⁻⁵ To improve the readability of this monograph, the proprietary name (*Viekira Pak*) for the ombitasvir/paritaprevir/ritonavir and dasabuvir combination pack will be used instead of a list of the individual drugs.

The combination of ombitasvir, paritaprevir, ritonavir, and ribavirin was studied in a small trial with patients infected with HCV genotype 1, 2, or 3; however, its efficacy, with or without ribavirin, in the treatment of HCV genotype 3-infected patients was less than that observed in those infected with HCV genotype 1 or 2.⁶ The *Viekira Pak* labeling indicates that safety and efficacy in treating patients with HCV genotypes other than genotype 1 have not been established.¹

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Table 1. Summary of direct-acting antivirals approved by the US Food and Drug Administration for the treatment of hepatitis C virus infections¹⁻⁵

Agent	Treatment of chronic genotype 1 HCV	Treatment of chronic genotype 1 HCV as a component of combination therapy	Treatment of HCV genotype 1, 2, 3, or 4 and HCV/HIV-1 as a component of combination therapy
<i>Viekira Pak</i>	X	X	
Ledipasvir/Sofosbuvir	X		
Sofosbuvir		X	X
Simeprevir		X	
Boceprevir		X	

CLINICAL PHARMACOLOGY

National surveillance estimates that as many as 3.2 million people in the United States have chronic HCV infection. Risk factors for HCV infection include use of injection drugs, receipt of clotting factors prior to 1987, receipt of blood transfusions or solid organ transplants prior to 1992, and long-term hemodialysis; at-risk populations include health care workers, persons with HIV infection, and children born to HCV-positive women.⁷ Previous treatment options included a combination of telaprevir, peginterferon, and ribavirin; treatment with this combination resulted in sustained viral response posttreatment at week 12 (SVR12) in 72% (95% confidence interval [CI], 68 to 75) of treatment-naïve genotype 1a and 80% (95% CI, 75 to 84) of treatment-naïve genotype 1b patients.⁸

The 4 components of *Viekira Pak* are ombitasvir, paritaprevir, ritonavir, and dasabuvir. Ombitasvir, paritaprevir, and dasabuvir are direct-acting antivirals, while ritonavir is an inhibitor of cytochrome P450 (CYP-450) 3A that increases the serum concentrations of paritaprevir. Paritaprevir is an inhibitor of NS3/4A protease that interrupts cleavage of the HCV polypeptide into NS3, NS4A, NS4B, NS5A, and NS5B, and therefore viral replication.¹ Doses greater than paritaprevir 200 mg plus ritonavir 100 mg reduce the incidence of resistance among HCV genotype 1.⁹ Ombitasvir is an inhibitor of NS5A that interrupts viral RNA replication and virion assembly.^{1,10} Resistance to ombitasvir is due to changes in the 28, 30, and 93 residues of the proteins.¹⁰ Dasabuvir is a nonnucleoside inhibitor of HCV polymerase that interrupts viral RNA replication.^{1,11} The most frequently occurring strains with resistance to dasabuvir are C316Y, M414T/V, Y448H/C, S556G,

and D559G; these mutants have less replicative ability compared with wild-type HCV.^{11,12} Dasabuvir has reduced activity against NS5B polymerases from HCV genotypes 2a, 2b, 3a, and 4a.¹

PHARMACOKINETICS

When taken as the *Viekira Pak*, the mean time to peak concentration of ombitasvir/paritaprevir/ritonavir and dasabuvir is between 4 and 5 hours. Accumulation is minimal for ombitasvir and dasabuvir, 1.5-fold for ritonavir, and 2-fold for paritaprevir; steady state is achieved after approximately 12 days of dosing. Administration of *Viekira Pak* with a moderate-fat (120 to 180 kcal of fat) or high-fat (540 kcal of fat) meal increases total exposure (area under the curve [AUC]). All 4 components are highly protein bound (between 97% and 99.9%), with volumes of distribution ranging from 16.7 to 396 L. Metabolism is by amide hydrolysis, CYP3A, CYP3A4, CYP3A5, CYP2D6, and CYP2C8. Elimination is primarily fecal (between 86.4% and 94.4%) for all 4 components.¹

When single oral doses of paritaprevir ranging from 300 to 900 mg were given alone, the maximal drug concentration (C_{max}) and AUC increased by more than 20-fold. Coadministration of paritaprevir and ritonavir 100 mg increased the AUC, C_{max} , and concentration 12 hours postdose by 50-, 30-, and 200-fold, respectively. Increasing the paritaprevir dose from 25 to 400 mg and administering it with ritonavir 100 mg increased the C_{max} and AUC of paritaprevir by 750-fold.¹³ Administration with a high- or moderate-fat meal increases the AUC of paritaprevir and ritonavir.¹ Protein binding of paritaprevir is between 97% and 98.6%, with a volume of distribution of 16.7 L; protein binding of ritonavir is greater than 99%, with a volume of distribution

of 21.5 L.¹ Repeated daily administration of paritaprevir and ritonavir led to accumulation 2 to 3 times that of single oral dosing.¹⁴ Repeated dosing of paritaprevir 300 mg and ritonavir 100 mg daily led to increases of $C_{\max}$ and AUC 100- and 50-fold greater than repeated dosing of paritaprevir 50 mg and ritonavir 100 mg twice daily.¹⁴ The primary metabolism of paritaprevir is by CYP3A4 and, to a lesser extent, CYP3A5; the primary metabolism of ritonavir is by CYP3A and, to a lesser extent, CYP2D6. Following a single oral dose of radiolabeled paritaprevir, 88% of radioactivity is recovered in the feces, primarily as metabolites. The mean half-life is 5.5 hours. Following single oral doses of radiolabeled ritonavir, 86.4% is recovered in the feces. When given with ombitasvir and paritaprevir, the mean plasma half-life of ritonavir is approximately 4 hours.¹

When given to healthy volunteers, single oral doses of ombitasvir 1.5 to 50 mg resulted in greater than proportional increases in $C_{\max}$ and total exposure (AUC), with no change in $C_{\max}$ or AUC from doses ranging from 50 to 100 mg.¹⁵ Administration with a moderate- or high-fat meal increases the absorption by 82% and 76%, respectively. Protein binding is approximately 99.9%, and the apparent volume of distribution is 50.1 L. Primary metabolism is by amide hydrolysis followed by oxidative metabolism.¹ The mean half-life is 18 to 26 hours for doses of at least 5 mg.^{10,15} Following a single oral dose of radiolabeled ombitasvir, 90.2% was excreted in the feces, primarily as unchanged drug. Mean half-life was between 21 and 25 hours.¹ Repeated daily dosing of 5 mg suggests that accumulation is expected, with an accumulation ratio of approximately 1.4.¹⁵ Coadministration of ombitasvir with ritonavir 100 mg increases the ombitasvir $C_{\max}$ (68%) and AUC (62%) at steady state compared with ombitasvir given alone.¹⁵

Dasabuvir is not expected to inhibit CYP enzymes or induce CYP3A4 expression in vivo.¹⁶

Single oral doses of dasabuvir produce a $C_{\max}$ at approximately 3 to 4 hours post dose.^{17,18} Both $C_{\max}$ and AUC increase in a dose-proportional manner, ranging from 10 to 1,200 mg,¹⁷ although increasing the dose from 400 mg to 1,200 or 1,600 mg produces a less than proportional increase in $C_{\max}$ and AUC.¹⁸ Administration with a moderate- or high-fat meal increased the absorption of dasabuvir.¹ Protein binding is greater than 99.5%, and volume of distribution is 396 L.¹ Multiple oral doses of dasabuvir at 200 or 400 mg twice daily did not produce significant accumulation after 10 days.¹⁹ Primary metabolism is by CYP2C8 and, to a lesser extent, CYP3A.

Following single oral doses, approximately 94.4% of radioactivity was recovered in feces, with 26% of radioactivity from unchanged dasabuvir. Mean half-life was between 5.5 and 6 hours.¹ In some studies, mean half-life ranged from 5 to 11 hours.^{17,18} In patients of Japanese descent, $C_{\max}$ and AUC were dose proportional from 400 to 1,600 mg.¹⁸ When adjusted for weight, there was no difference in pharmacokinetic parameters between US and Japanese subjects.¹⁸

COMPARATIVE EFFICACY

Indication: Chronic Infection With Hepatitis C Virus Genotypes 1a and 1b With or Without Ribavirin

Guidelines

Guideline: Recommendations for testing, managing, and treating hepatitis C

Reference: American Association for the Study of Liver Diseases and Infectious Diseases Society of America, 2014²⁰

Comments: The recommended initial treatment options for patients with HCV genotype 1 include ombitasvir/paritaprevir/ritonavir plus dasabuvir with or without ribavirin, ledipasvir/sofosbuvir, or sofosbuvir plus simeprevir with or without ribavirin. The guidelines recommend against the use of sofosbuvir plus ribavirin, or peginterferon plus ribavirin, with or without sofosbuvir, simeprevir, telaprevir, or boceprevir; the guidelines also recommend against the use of monotherapy with any drug. Retreatment options for patients in whom peginterferon plus ribavirin combinations have failed are similar to initial treatment options. Treatment of patients with cirrhosis is similar to initial treatment options. In patients with HCV/HIV-1 coinfection, ombitasvir/paritaprevir/ritonavir plus dasabuvir, ledipasvir/sofosbuvir, and simeprevir should be used with antiretroviral drugs with which they have limited interactions. Interruption of antiretroviral therapy for HCV therapy is not recommended. In patients with HCV genotype 1 in the allograft after transplant and without cirrhosis, ombitasvir/paritaprevir/ritonavir plus dasabuvir combinations are recommended.

Studies

Drug: *Viekira Pak* plus Placebo vs *Viekira Pak* plus Ribavirin

Reference: Andreone P, et al, 2014 (PEARL-II trial)²¹

Study Design: Randomized, double-blind, placebo-controlled, historical control, multicenter study

Study Funding: AbbVie Inc

Patients: One hundred eighty-six treatment-experienced patients 18 to 70 years of age with HCV genotype 1b and RNA level greater than 10,000 units/mL. Exclusion criteria included evidence of cirrhosis, HIV or hepatitis B virus (HBV) infection, or HCV infection other than genotype 1b. Baseline characteristics follow for the *Viekira Pak* without ribavirin group and the *Viekira Pak* with ribavirin group, respectively, as applicable: Mean age was 54 years for each group; 60% and 50% were male; 91% and 92% of patients were White; 93% and 89% had a non-CC IL28B mutation; mean HCV RNA level was 6.48 and 6.56 log₁₀ units/mL; and 64% and 70% had baseline fibrosis F0 or F1. Response to previous treatment included the following: 35% were null responders in each group, 37% relapsed in each group, and 28% and 29%, respectively, were partial responders.

Intervention: Patients were randomized 1:1 to receive *Viekira Pak* plus placebo or *Viekira Pak* plus ribavirin (1,000 mg for patients weighing less than 75 kg, or 1,200 mg in divided doses for patients weighing 75 kg or more) for 12 weeks.

Results

Primary Endpoint(s)

- Proportion of patients achieving SVR12 was 96.6% (95% CI, 92.8 to 100) with *Viekira Pak* plus ribavirin and 100% (95% CI, 95.9% to 100%) with *Viekira Pak* plus placebo; both groups were superior to historical rate with telaprevir plus peginterferon and ribavirin.

Secondary Endpoint(s)

- Treatment difference between *Viekira Pak* plus placebo and *Viekira Pak* plus ribavirin was 3.4% (95% CI, -0.4% to 7.2%), which met noninferiority of -10.5%.
- Proportion of patients with hemoglobin less than the lower limit of normal (LLN) was 42% with *Viekira Pak* plus ribavirin compared with 5.5% with *Viekira Pak* alone ($P < .001$).

Endpoint(s)

- Adverse events occurring at a higher rate with *Viekira Pak* plus ribavirin compared with the *Viekira Pak* alone were fatigue (31.9% vs 15.8%, respectively; $P = .015$), nausea (20.9% vs 6.3%, respectively; $P = .005$), insomnia (14.3% vs 3.2%, respectively; $P = .008$), anemia

(11% vs 0%, respectively; $P < .001$), elevated blood bilirubin (8.8% vs 0%, respectively; $P = .003$), rash (8.8% vs 1.1%, respectively; $P = .017$), and total bilirubin greater than 3 times the upper limit of normal (ULN) (8.8% vs 0%, respectively; $P = .003$).

Comments: This was a phase 3 trial that included treatment-experienced HCV genotype 1b patients only. The primary endpoint compared the new combination with trials using telaprevir plus peginterferon and ribavirin. Two patients discontinued treatment early due to adverse events and showed resistance to combination medication at posttreatment weeks 4 and 12. Stratification was based on null response, partial response, and relapse to previous peginterferon plus ribavirin treatment. The previous type of nonresponse did not correlate with efficacy of *Viekira Pak* with or without ribavirin. In a phase 2 study including liver transplant patients, 97% (33 of 34) achieved SVR12 and sustained viral response at 24 weeks (SVR24) after receiving *Viekira Pak* plus ribavirin for 24 weeks.²² No patients experienced liver rejection, and all were able to maintain treatment with either cyclosporine or tacrolimus after dosing adjustments.²²

Reference: Ferenci P, et al, 2014 (PEARL-IV trial)⁸

Study Design: Randomized, double-blind, active-comparator, placebo-controlled, historical control, multicenter study

Study Funding: AbbVie Inc

Patients: Three hundred five treatment-naïve patients 18 to 70 years of age with HCV genotype 1a and RNA level greater than 10,000 units/mL. Exclusion criteria included evidence of cirrhosis, HIV or HBV infection, or HCV infection other than genotype 1a. Baseline characteristics follow for the *Viekira Pak* without ribavirin group and the *Viekira Pak* with ribavirin group, respectively: Mean age was 52 and 51 years; 70% and 63% were male; 86% and 83% of patients were White; 63% and 64% had a Metavir fibrosis score of 0 or 1; 31% and 31% had IL28B CC genotype; and 92% and 84% had HCV RNA at least 800,000 units/mL.

Intervention: Patients were randomized 1:2 to receive *Viekira Pak* plus placebo or *Viekira Pak* plus ribavirin (1,000 mg for patients weighing less than 75 kg, or 1,200 mg in divided doses for patients weighing 75 kg or more) for 12 weeks.

Results**Primary Endpoint(s)**

- Proportion of patients achieving SVR12 (HCV RNA level less than 25 units/mL) was 97% (95% CI, 93.7% to 100%) with *Viekira Pak* plus ribavirin and 90.2% (95% CI, 86.2 to 94.3) with *Viekira Pak* alone; both regimens were superior to historical treatment with telaprevir plus peginterferon and ribavirin.

Secondary Endpoint(s)

- *Viekira Pak* alone did not meet noninferiority to *Viekira Pak* plus ribavirin; treatment difference between *Viekira Pak* and *Viekira Pak* plus ribavirin was -6.8% (95% CI, -12 to -1.5).

Endpoint(s)

- Adverse events more frequently reported with *Viekira Pak* plus ribavirin versus *Viekira Pak* alone included insomnia (17% vs 7.8%, respectively; $P = .02$), hemoglobin less than the LLN (42% vs 3.9%, respectively; $P < .001$), and hemoglobin less than or equal to 10 g/dL (4% vs 0%, respectively; $P = .01$).

Comments: This was a phase 3 pivotal trial. Stratification was based on IL28B CC genotype; allocation was blinded. Patients were followed and blood was drawn up to 48 weeks after the last dose, but results were not reported. Paritaprevir and ritonavir plus peginterferon and ribavirin were compared with placebo plus peginterferon and ribavirin in a dose-ranging study.²³ All arms containing paritaprevir and ritonavir had higher rates of SVR12 compared with the placebo arm.²³ Ombitasvir was studied in a similar manner and found to be more effective than placebo at reducing HCV RNA loads after 3 days of monotherapy.¹⁰ A small trial to assess the efficacy of ombitasvir/paritaprevir/ritonavir with or without ribavirin in patients with HCV genotypes 1, 2, or 3 was reported.⁶ The data suggest that the combination is effective with or without ribavirin in producing SVR12 and SVR24 for patients with HCV genotypes 1 and 2, but not genotype 3. The combination was only effective in producing SVR12 or SVR24 in combination with ribavirin in genotype 3.⁶

Reference: Ferenci P, et al, 2014 (PEARL-III trial)⁸

Study Design: Randomized, double-blind, active-comparator, placebo-controlled, historical control, multicenter study

Study Funding: AbbVie Inc

Patients: Four hundred nineteen patients with HCV genotype 1b. Other inclusion and exclusion criteria were identical to the PEARL-IV trial. Baseline characteristics follow for the *Viekira Pak* without ribavirin group and the *Viekira Pak* with ribavirin group, respectively: Mean age was 48 and 49 years; 51% and 41% were male; 94% and 94% of patients were White; 72% and 68% had Metavir fibrosis score of 0 or 1; 21% and 21% had IL28B CC genotype; and 76% and 71% had HCV RNA at least 800,000 units/mL.

Intervention: Patients were randomized 1:1 to receive *Viekira Pak* plus placebo or *Viekira Pak* plus ribavirin at the same doses as in the PEARL-IV trial.

Results**Primary Endpoint(s)**

- Proportion of patients achieving SVR12 was 99.5% (95% CI, 98.6% to 100%) with *Viekira Pak* plus ribavirin and 99% (95% CI, 97.7% to 100%) with *Viekira Pak* alone; both regimens were superior to historical treatment with telaprevir plus peginterferon and ribavirin.

Secondary Endpoint(s)

- *Viekira Pak* alone was noninferior to *Viekira Pak* plus ribavirin; treatment difference was -0.5% (95% CI, -2.1% to 1.1%).

Endpoint(s)

- Adverse events more frequently reported with *Viekira Pak* plus ribavirin than with *Viekira Pak* alone included pruritus (11.9% vs 5.3%, respectively; $P = .02$), nausea (11% vs 4.3%, respectively; $P = .02$), insomnia (9% vs 3.3%, respectively; $P = .02$), hemoglobin less than the LLN (51.2% vs 3.4%, respectively; $P < .001$), hemoglobin of 10 g/dL or less (9% vs 0%, respectively; $P < .001$), and total bilirubin greater than 3 times the ULN (12% vs 0.5%, respectively; $P = .003$).

Comments: This was a phase 3 trial identical to the PEARL-IV trial. The PEARL-III study included only patients with genotype 1b and showed similar rates of cure with or without ribavirin.

Drug: *Viekira Pak* vs Placebo

Reference: Feld JJ, et al, 2014 (SAPPHIRE-I trial)²⁴

Study Design: Randomized, double-blind, placebo-controlled, historical control, multicenter study

Study Funding: AbbVie Inc

Patients: Six hundred thirty-six (modified intent-to-treat population, $n = 631$) treatment-naïve

patients 18 to 70 years of age with chronic HCV genotype 1 infection, RNA level greater than 10,000 units/mL, and no cirrhosis. Exclusion criteria include HBV infection, HIV antibodies, recent history of drug or alcohol abuse, and a history of uncontrolled seizures or uncontrolled diabetes. Baseline characteristics of the active and placebo arms follow, respectively: 57% and 46% were male; 91% and 91% were White; mean age was 49 and 51 years; 23% and 27% had fibrosis scores of 2 or greater; 30% and 32% had IL28B CC genotype; 68% and 67% had HCV genotype 1a; and mean HCV RNA tier was 6.4 and 6.47 log₁₀ units/mL.

Intervention: Patients were randomized 3:1 to receive *Viekira Pak* plus ribavirin (1,000 mg for patients weighing less than 75 kg, or 1,200 mg in divided doses for patients weighing 75 kg or more) or matching placebo for 12 weeks. After 12 weeks, patients in the placebo arm crossed over to active treatment.

Results

Primary Endpoint(s)

- Proportion of patients achieving SVR12 with *Viekira Pak* plus ribavirin was 96.2% (95% CI, 94.9% to 97.9%) achieving both noninferiority and superiority to historical controls.

Secondary Endpoint(s)

- Proportion of patients with genotype 1a achieving SVR12 was 95.3% (95% CI, 93% to 97.6%).
- Proportion of patients with genotype 1b achieving SVR12 was 98% (95% CI, 95.8% to 100%).
- Rate of normalization of alanine aminotransferase (ALT) was 97% with *Viekira Pak* plus ribavirin compared with 14.9% with placebo ($P < .001$).

Endpoint(s)

- Proportion of patients achieving SVR12 with IL28B CC or non-CC was 96.5% and 96%, respectively.
- Proportion of patients with reduction in hemoglobin between 10 g/dL and the LLN was 47.5% in the *Viekira Pak* plus ribavirin arm and 2.5% in the placebo arm.
- High body mass index was associated with a reduced achievement of SVR12 (odds ratio [OR], 0.89; $P = .02$).
- Race, baseline fibrosis score, and baseline HCV RNA level less than 800,000 units/mL or 800,000 units/mL or greater did not have an impact on rates of achieving SVR12.

- One patient (0.2%) in the active arm experienced virologic failure during treatment; 7 patients (1.5%) in the active arm had relapsed by posttreatment week 12.
- The most frequently reported adverse events were fatigue and headache.

Comments: This was a phase 3 trial. Blinded allocation was used. Patients and investigators were blinded to laboratory findings during the initial 12 weeks of treatment. Ribavirin dose reduction was required in 5.5% of patients due to adverse reactions. A separate phase 2 study including treatment-naïve HCV patients receiving *Viekira Pak* plus ribavirin for 12 weeks yielded a 96% SVR24 rate in 79 patients.²⁵

Limitations: This is an interim report of the primary endpoint. Study is ongoing for 48-week follow-up.

Drug: *Viekira Pak* plus Ribavirin vs Placebo

Reference: Zeuzem S, et al, 2014 (SAPPHIRE-II trial)²⁶

Study Design: Randomized, double-blind, placebo-controlled, multicenter study

Study Funding: AbbVie Inc

Patients: Three hundred ninety-four patients 18 to 70 years of age with chronic HCV genotype 1 infection, HCV RNA titer greater than 10,000 units/mL, prior treatment with peginterferon and ribavirin therapy, and without cirrhosis. Exclusion criteria included nonresponse to triple therapy of peginterferon, ribavirin, and a protease inhibitor; positive hepatitis B antibodies; HIV-1 antibodies; advanced fibrosis; and positive screening for either drugs or alcohol. Baseline characteristics for active and placebo arms follow, respectively: Mean age was 52 and 55 years; 56% and 62% were male; 46% and 34% were in North America; 32% and 33% had a fibrosis score of F2 or F3; 58.2% and 58.8% had HCV genotype 1a; 29% and 29.9% had experienced a prior relapse; 21.9% and 21.6% were partial responders; and 49.2% and 48.5% were null responders.

Intervention: Patients were randomized 3:1 to receive *Viekira Pak* plus ribavirin (1,000 mg for patients weighing less than 75 kg, or 1,200 mg in divided doses for patients weighing 75 kg or more) or matching placebo for 12 weeks. After 12 weeks, patients in the placebo arm crossed over to active treatment.

Results**Primary Endpoint(s)**

- Proportion of patients on active treatment achieving SVR12 was 96.3% (95% CI, 94.2% to 98.4%); noninferiority and superiority were achieved over historical rates.

Secondary Endpoint(s)

- No patient experienced virologic failure during treatment.
- All patients completing at least 77 days of therapy had HCV RNA less than 25 units/mL at the end of treatment.
- Proportion of patients with posttreatment viral relapse was 2.4%.
- Proportion of patients with normalization of ALT was 96.9% in the *Viekira Pak* plus ribavirin arm and 12.8% in the placebo arm ($P < .001$).

Endpoint(s)

- The most commonly reported adverse events were headache, fatigue, and nausea.
- Adverse events occurring at a higher rate in the active arm compared with the placebo arm included pruritus, anemia, decreased hemoglobin, and vomiting.

Comments: This was a phase 3 trial. Retreatment of patients with previous failure on peginterferon and ribavirin showed efficacy with regard to SVR12. Response was similar across subgenotypes 1a or 1b and similar across previous types of treatment failure. A separate phase 2 study, including treatment-experienced HCV patients receiving *Viekira Pak* plus ribavirin for 12 weeks, resulted in a 93% SVR24 rate in 45 patients.²⁵ In patients coinfecting with HCV/HIV-1 treated with *Viekira Pak* plus ribavirin and either atazanavir- or raltegravir-based antiretroviral therapy for 12 weeks, SVR12 was seen in 93.8% and 93.3%, respectively.²⁷

Limitations: This was an interim, primary endpoint analysis of an ongoing study.

Drug: *Viekira Pak* with Ribavirin

Reference: Poordad F, et al, 2014 (TURQUOISE-II trial)²⁸

Study Design: Randomized, open-label, historical control, multicenter study

Study Funding: AbbVie Inc

Patients: Three hundred eighty-one treatment-experienced and treatment-naïve patients (modified intent-to-treat population, $n = 380$) with HCV genotype 1, cirrhosis, HCV RNA titer greater than 10,000 units/mL, Child-Pugh score less than 7

(class A), platelet count greater than 60,000/mm³, albumin at least 2.8 g/dL, total bilirubin less than 3 mg/dL, international normalized ratio of 2.3 or less, and serum alpha-fetoprotein level of 100 ng/mL or less. Key exclusion criteria included past clinical evidence of Child-Pugh class B or C, treatment with direct-acting antiviral agents (eg, telaprevir, boceprevir), and diagnosis of hepatocellular carcinoma. Baseline characteristics of the 12- and 24-week groups follow, respectively, as applicable: Mean age in both groups was 57 years; 70% in both groups were male; 96% and 94% of patients were White; 67% and 70% had HCV genotype 1a; 83% and 80% had non-CC genotype; 62% and 63% were null responders; 24% in each group had previously relapsed; median platelet count was 140,000/mm³ and 142,500/mm³; and serum albumin was 40 g/L and 39 g/L.

Intervention: Patients were randomized 1:1 to receive *Viekira Pak* plus ribavirin (1,000 mg for patients weighing less than 75 kg, or 1,200 mg in divided doses for patients weighing 75 kg or more) for 12 or 24 weeks.

Results**Primary Endpoint(s)**

- Proportion of patients achieving SVR12 in the 12-week group was 91.8% (97.5% CI, 87.6% to 96.1%); SVR12 achieved in the 24-week group was 95.9% (97.5% CI, 92.6% to 99.3%). Both results were noninferior and superior to historical controls; efficacy at 12 weeks compared with 24 weeks was not different ($P = .09$).

Secondary Endpoint(s)

- Proportion of previously untreated patients in the 12-week group with SVR12 was 94.2%; in the 24-week group, SVR12 was 94.6%.
- Proportion of patients with HCV genotype 1a in the 12-week group with SVR12 was 88.6%; in the 24-week group, SVR12 was 94.2%.
- Proportion of patients with HCV genotype 1b in the 12-week group with SVR12 was 98.5%; in the 24-week group, SVR12 was 100%.
- Proportion of previously treated patients achieving SVR12 and based on previous failure was 96.6% versus 100% for relapse, 94.4% versus 100% for partial response, and 86.7% versus 95.2% for null response in the 12- and 24-week groups, respectively.
- Proportion of patients with virologic failure during treatment or relapse after treatment was

6.2% and 2.3% in the 12-week and 24-week groups, respectively; proportion of patients with relapse was higher in the 12-week arm compared with the 24-week arm (5.9% vs 0.6%; *P* value not provided).

Endpoint(s)

- The most commonly reported severe adverse reactions were elevated bilirubin levels and decreased hemoglobin levels.
- Fatigue and dyspnea were more common in the 24-week arm compared with the 12-week arm.
- Elevated ALT levels were more common in the 12-week arm compared with the 24-week arm.

Comments: This was a phase 3 trial. Hierarchical stratification began with previous treatment with peginterferon/ribavirin. Previously untreated patients were stratified by HCV genotype 1 sub-genotype and IL28B genotype; previously treated patients were stratified by treatment failure (null response, partial response, and viral relapse). Analysis showed that patients without a response to previous treatment with peginterferon and injection drug use had a decreased likelihood of achieving SVR12. One small study used only paritaprevir, ritonavir, dasabuvir, and ribavirin.²⁹ This study included 17 previously treated patients, of whom 8 (47%) achieved SVR12 and subsequently SVR posttreatment at week 36.²⁹

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

The contraindications, warnings, precautions, and use in special populations for direct-acting HCV antivirals are provided in **Table 2**.¹⁻⁵

Contraindications

If *Viekira Pak* is administered with ribavirin, the contraindications pertaining to ribavirin apply to the combination therapy. *Viekira Pak* is contraindicated in patients with severe hepatic impairment due to risk of toxicity.¹ *Viekira Pak* is also contraindicated in patients with known hypersensitivity to ritonavir.¹

Coadministration of *Viekira Pak* with multiple medications that are heavily dependent on the CYP3A metabolic pathway is contraindicated due to potentially reduced efficacy or toxicity of *Viekira Pak* or of concomitant medications.¹

Coadministration of drugs that are strong inducers of CYP3A and CYP2C8 may reduce the efficacy of *Viekira Pak*.¹

Drugs that are strong inhibitors of CYP2C8 may increase dasabuvir plasma concentration and increase the risk of QT prolongation.¹

The medications leading to potentially reduced efficacy of *Viekira Pak*, and therefore contraindicated, include carbamazepine, phenytoin, phenobarbital, rifampin, and St. John's wort.¹

Coadministration with the following drugs may lead to toxicity and is therefore contraindicated: alfuzosin (hypotension); gemfibrozil (QT prolongation); ergotamine (acute ergot toxicity); dihydroergotamine, ergonovine, methylergonovine, ethinyl estradiol (potential ALT elevations); lovastatin (myopathy); simvastatin (rhabdomyolysis); pimozide (cardiac arrhythmias); efavirenz (elevated liver enzymes); sildenafil (*Revatio* indicated for pulmonary arterial hypertension: visual disturbances, hypotension, priapism, and syncope); triazolam (prolonged and increased sedation); and orally administered midazolam (prolonged and increased sedation).¹

Additionally, the prescribing information for ritonavir recommends against coadministration of amiodarone, flecainide, propafenone, quinidine, voriconazole, and cisapride.³⁰ See **Table 3** for clinical comments and management of drug-drug interactions.

Warnings and Precautions

Use of *Viekira Pak* was associated with elevations of ALT exceeding 5 times the ULN at a frequency of approximately 1% across clinical trials. Most elevations were asymptomatic, occurred within the first 4 weeks of treatment, and declined within 2 to 8 weeks with continued dosing. Elevations were significantly more frequent in females concomitantly treated with ethinyl estradiol-containing products, including oral contraceptives. Alternative methods (eg, progesterone only, nonhormonal) of contraception are recommended during treatment with *Viekira Pak*. Ethinyl estradiol-containing products can be restarted approximately 2 weeks after discontinuation of *Viekira Pak*.¹

Women using estrogens other than ethinyl estradiol had elevations in ALT similar to patients not treated with hormone replacement therapy. Due to the limited number of patients using these estrogens, data are inconclusive regarding the risk of elevated ALT. Patients treated with estrogens other than ethinyl estradiol (eg, estradiol, conjugated estrogens) should have hepatic laboratory testing performed within the first 4 weeks of starting treatment.¹

Table 2. Summary of contraindications, warnings, precautions, and use in special populations for direct-acting antivirals^{1,2,3,4,5}

	<i>Viekira Pak</i>	Sofosbuvir plus ledipasvir	Sofosbuvir	Simeprevir	Boceprevir
<i>Contraindications</i>					
Hypersensitivity	X				X
Coadministration with drugs dependent on CYP3A	X				X
Coadministration with strong inducers of CYP3A and CYP2C8	X				
Coadministration with strong inhibitors of CYP2C8	X				
Coadministration with ethinyl estradiol	X				
Severe hepatic impairment	X				
Risks from combination medications (ribavirin, peginterferon)	X		X	X	X
<i>Warnings and precautions</i>					
Hepatic reactions	X				
Allergic reaction					X
Risk from drugs taken in combination (pregnancy, anemia, neutropenia, pancytopenia)	X		X	X	X
Photosensitivity				X	
Rash				X	
Sulfa allergy				X	
Reduced therapeutic effect due to P-glycoprotein inducers		X	X		
Combination with other products containing sofosbuvir			X		
Drug interactions	X			X	X
Risk of HIV-1 protease inhibitor resistance in HIV-1 coinfecting patients	X				
<i>Special populations</i>					
Pregnancy	Category B (ribavirin Category X)	Category B	Category X because of ribavirin or peginterferon alfa/ribavirin combination therapy	Category C	Category B (Category X because of ribavirin or peginterferon)

(continued)

Table 2. Summary of contraindications, warnings, precautions, and use in special populations for direct-acting antivirals^{1,2,3,4,5} (CONT.)

	<i>Viekira Pak</i>	Sofosbuvir plus ledipasvir	Sofosbuvir	Simeprevir	Boceprevir
Breast-feeding	Use caution	Use caution	Not recommended	Not recommended	Not recommended
Pediatric	Not established	Not established	Not established	Not established	Not established
Elderly	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
Renal impairment	No adjustment	No adjustment	No adjustment; not approved when CrCl < 30 mL/minute or in end-stage renal disease	No adjustment	No adjustment
Hepatic impairment	Mild impairment: no adjustment; moderate impairment: not recommended; severe impairment: contraindicated	No adjustment	No adjustment	No adjustment	No adjustment
Liver transplantation	Effective and approved	Not established	Not established	Not established	Not established

If *Viekira Pak* is administered with ribavirin, the contraindications, warnings, precautions, and risks associated with ribavirin apply to the combination therapy. Refer to the ribavirin prescribing information for more information.¹

Multiple drug-drug interactions between *Viekira Pak* and other medications may occur. These interactions may lead to unsafe levels of concomitant medications or loss of efficacy of *Viekira Pak*. Recommendations for managing these drug-drug interactions are provided in **Table 3**.^{1,19,22}

Ritonavir is a protease inhibitor sometimes used in HIV-1. In HIV-1/HCV coinfecting patients, use of *Viekira Pak* alone may lead to development of protease inhibitor resistance by HIV. Patients coinfecting with HIV-1/HCV should receive adequate combination antiretroviral therapy to reduce the risk of protease inhibitor resistance.¹

Cases of allergic reactions have been reported in patients treated with ritonavir; *Viekira Pak* is contraindicated in patients with known hypersensitivity to ritonavir (eg, toxic epidermal necrolysis, Stevens-Johnson syndrome).^{1,30}

Safety and efficacy of *Viekira Pak* have not been established in patients with HCV genotypes other

than genotype 1.¹ Safety and efficacy of *Viekira Pak* have not been established in patients with HCV genotype 2 or HCV genotype 3.^{1,6} Combinations of ombitasvir, paritaprevir, and ritonavir without ribavirin were shown to be ineffective in a small study with patients infected with HCV genotype 3.⁶

Generally, patients with coinfection of HBV or HIV were excluded from pivotal trials.^{8,21,22} One open-label study reported use of *Viekira Pak* in patients coinfecting with HCV/HIV-1.²⁷ The prescribing information does not highlight special precautions other than the use of adequate antiretroviral therapy and management of drug-drug interactions in these patients.¹ Safety and efficacy have not been determined in patients coinfecting with HBV.

Viekira Pak when administered alone is classified as Pregnancy Category B; there are no adequate and well-controlled studies in pregnant women. In mice and rabbits treated throughout pregnancy, teratogenicity was not seen at supratherapeutic doses.¹

There is a pregnancy registry for patients coinfecting with HCV/HIV-1 and taking antivirals. It is recommended that physicians register patients who qualify.¹

Table 3. Clinically significant drug-drug (established or potential) interactions between *Viekira Pak* and concomitant medications^{1,19,22}

Concomitant drug class: Drug name	Effect on concentration	Clinical comments/recommendations
<i>Antiarrhythmics:</i>		
Amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↑ Antiarrhythmics	Use caution; monitor therapeutic concentrations (if available)
<i>Antifungals:</i>		
Ketoconazole	↑ Ketoconazole	Limit ketoconazole dosage to 200 mg per day
Voriconazole	↓ Voriconazole	Coadministration not recommended; use only if benefit of voriconazole outweighs risk
<i>Calcium channel blockers:</i>		
Amlodipine	↑ Amlodipine	Monitoring recommended; consider reducing amlodipine dose
<i>Corticosteroids (inhaled/nasal):</i>		
Fluticasone (propionate, furoate [unclear])	↑ Fluticasone	Elevated levels of fluticasone may suppress endogenous cortisol production and reduce serum cortisol; alternative corticosteroids are recommended, particularly for long-term use
<i>Diuretics:</i>		
Furosemide	↑ Furosemide (C_{max})	Monitoring recommended; individualize dose of furosemide according to patient response
<i>HIV antiviral drugs:</i>		
Atazanavir/Ritonavir	↑ Paritaprevir	Discontinue combination of atazanavir/ritonavir; use of atazanavir 300 mg alone is recommended
Darunavir/Ritonavir	↓ Darunavir (C_{trough})	Coadministration not recommended
Lopinavir/Ritonavir	↑ Paritaprevir	Coadministration not recommended
Rilpivirine	↑ Rilpivirine	Risk of QT prolongation; coadministration not recommended
<i>HMG-CoA reductase inhibitors (statins):</i>		
Rosuvastatin	↑ Rosuvastatin	Limit dose of rosuvastatin to 10 mg per day
Pravastatin	↑ Pravastatin	Limit dose of pravastatin to 40 mg per day
<i>Immunosuppressants:</i>		
Cyclosporine	↑ Cyclosporine	Reduce cyclosporine dose to one-fifth of the dose before administering <i>Viekira Pak</i> ; measure serum cyclosporine to guide dose adjustments; monitor renal function and for signs of cyclosporine toxicity
Tacrolimus	↑ Tacrolimus	Do not administer tacrolimus on the day <i>Viekira Pak</i> is initiated; reduce tacrolimus dose based on serum tacrolimus levels
<i>Long-acting beta-adrenoceptor agonist:</i>		
Salmeterol	↑ Salmeterol	Risk of QT prolongation, palpitations, and sinus tachycardia; coadministration not recommended
<i>Narcotic analgesics:</i>		
Buprenorphine/Naloxone	↑ Buprenorphine ↑ Norbuprenorphine	No dose adjustment recommended; monitor for sedation and cognitive effects

(continued)

Table 3. Clinically significant drug-drug (established or potential) interactions between *Viekira Pak* and concomitant medications^{1,19,22} (CONT.)

Concomitant drug class: Drug name	Effect on concentration	Clinical comments/recommendations
<i>Proton pump inhibitors:</i>		
Omeprazole	↓ Omeprazole	May reduce efficacy of omeprazole. Consider increasing dose of omeprazole; doses of omeprazole greater than 40 mg per day are not recommended
<i>Sedatives/Hypnotics:</i>		
Alprazolam	↑ Alprazolam	Clinically monitor; individualize dose according to response

Ribavirin is classified as Pregnancy Category X. Use of ribavirin during pregnancy is contraindicated. Avoid pregnancy during treatment with ribavirin and for at least 6 months following cessation of therapy. Two forms of effective contraception should be used by men and women of childbearing age who are undergoing treatment with ribavirin.³¹

It is not known whether the components of *Viekira Pak* are excreted in human breast milk. Ombitasvir, paritaprevir, and dasabuvir were observed in the milk of lactating rats and did not have a significant impact on the pups. When deciding to continue or discontinue breast-feeding and/or *Viekira Pak*, consider the benefits of therapy with *Viekira Pak*, the developmental and health benefits of breast-feeding, the risks of *Viekira Pak* to the infant, and the risks of the underlying condition of the mother.¹

It is not known whether ribavirin is excreted in human milk. Due to potential for severe adverse events, a decision should be made to discontinue breast-feeding or ribavirin.³¹

Safety and efficacy of *Viekira Pak* have not been established in pediatric patients.¹

No difference in safety and efficacy were seen when comparing patients younger than 65 years with patients 65 years and older. No dose adjustment is recommended for patients 65 years and older, although the risk of increased sensitivity cannot be ruled out.¹

No dosage adjustment is recommended in patients with mild hepatic impairment (Child-Pugh class A). *Viekira Pak* is not recommended in patients with moderate hepatic impairment (Child-Pugh class B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh class C).¹

No dosage adjustment is recommended for patients with mild, moderate, or severe renal impairment. *Viekira Pak* has not been studied in patients on

dialysis.¹ Ribavirin has not been studied in patients with creatinine clearance (CrCl) less than 50 mL/minute and should not be used in that population.³¹

ADVERSE REACTIONS

The most commonly reported adverse events reported by patients undergoing therapy with *Viekira Pak* plus ribavirin included nausea, headache, asthenia, insomnia, fatigue, pruritus, other skin reactions, decreased hemoglobin, and elevated bilirubin.^{1,6,8,21,24,28} The rate of these adverse events was higher in patients treated with *Viekira Pak* plus ribavirin compared with those treated with *Viekira Pak* alone. **Table 4** summarizes the rates of adverse events for various treatment regimens.¹

Other adverse events included rash-related events. Most cases were mild, and there were no cases of Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, or drug rash with eosinophilia and systemic symptoms.¹

Elevations in serum ALT at least 5 times the ULN occurred in approximately 1% of all subjects treated with *Viekira Pak*. Elevations were usually asymptomatic, occurred during the first 4 weeks of treatment, and resolved without a change in therapy. Elevations of ALT were not generally associated with elevations in bilirubin or presence of cirrhosis.¹ The risk of elevated ALT was increased in women taking ethinyl estradiol and other estrogen-containing products.¹

Elevations in serum bilirubin at least 2 times the ULN occurred in 15% of patients treated with *Viekira Pak* plus ribavirin and in 2% of patients treated with *Viekira Pak* alone. Elevations peaked by study week 1 and resolved without a change in therapy.¹

Decreases in hemoglobin were seen in patients treated with *Viekira Pak*. The mean decrease in all patients treated with *Viekira Pak* plus ribavirin was

Table 4. Rates of adverse events for 12-week placebo- and active-controlled trials¹

Adverse events		
Reported in ≥ 5% of patients in placebo-controlled trials	<i>Viekira Pak</i> plus ribavirin (<i>n</i> = 770)	Placebo (<i>n</i> = 255)
Fatigue	34%	26%
Nausea	22%	15%
Pruritus	18%	7%
Skin reactions	16%	9%
Insomnia	14%	8%
Asthenia	14%	7%
Reported in ≥ 5% of patients with <i>Viekira Pak</i> plus ribavirin compared with <i>Viekira Pak</i> alone	<i>Viekira Pak</i> plus ribavirin (<i>n</i> = 401)	<i>Viekira Pak</i> (<i>n</i> = 509)
Nausea	16%	8%
Pruritus	13%	7%
Insomnia	12%	5%
Asthenia	9%	4%

2.4 g/dL, and the mean decrease in patients treated with *Viekira Pak* alone was 0.5 g/dL. Decreases frequently occurred within the first 2 weeks of treatment and continued to decline through week 3. Hemoglobin levels stayed low and returned to baseline by posttreatment week 4.¹

DRUG INTERACTIONS

The components of *Viekira Pak* are inhibitors of multiple enzymes, including CYP3A, UGT1A1, BCRP, OATP1B1, and OATP1B3. Potential drug interactions may lead to elevations of serum concentrations of various substrates of CYP3A, UGT1A1, BCRP, OATP1B1, or OATP1B3.¹

Potential drug interactions that may increase the serum concentration of one or more components of *Viekira Pak* include strong inhibitors of CYP3A, CYP2C8, P-glycoprotein, BCRP, OATP1B1, or OATP1B3.¹

The following medications require no dosage adjustment when administered with *Viekira Pak*: digoxin, duloxetine, emtricitabine/tenofovir disoproxil fumarate, escitalopram, methadone, progestin-only contraceptives, raltegravir, warfarin, and zolpidem.¹ Coadministration of some medications with *Viekira Pak* is contraindicated (see Contraindications, Warnings, and Precautions). For a summary of clinically

manageable interactions with recommendations for management, see Table 3.^{1,19,22}

RECOMMENDED MONITORING

Prior to treatment, phylogenetic analysis should be performed to ensure the patient has an infection of HCV genotype 1.^{8,21,24} Additional screening should include the subtype (1a or 1b) because it guides the use of ribavirin.^{1,8}

Patients should be strictly monitored for adherence and encouraged to complete treatment regimens. Short durations of treatment (eg, 10 to 30 days) may induce resistance to the components of *Viekira Pak*.²¹

HCV RNA titers may decrease as soon as 4 weeks into therapy, but patients should be counseled to continue taking the medication for the full 12-week duration.^{24,32} HCV RNA titers after 4 weeks of treatment are not strongly correlated with SVR12.²⁹

Monitoring of liver enzymes prior to treatment, within 4 weeks of initiating therapy, and when clinically indicated is recommended.^{1,8,21,24}

Female patients of childbearing potential should be tested for pregnancy before, during, and up to 6 months after therapy with ribavirin due to the potential for teratogenesis.^{1,31}

DOSING

The recommended dose requires the use of 2 different tablets. One tablet contains ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg, which is taken as 2 tablets once daily (in the morning) with food. The other tablet contains dasabuvir 250 mg, which is taken as 1 tablet twice daily (morning and evening) with food. If used in conjunction with ribavirin, the recommended dose of ribavirin is weight-based (1,000 mg per day in 2 divided doses with food for patients weighing less than 75 kg, and 1,200 mg per day in 2 divided doses with food for patients weighing 75 kg or more). Refer to the ribavirin prescribing information for recommended dosing adjustments in special populations.¹

For patients with genotype 1a without cirrhosis, the recommended duration of treatment with *Viekira Pak* plus ribavirin is 12 weeks.¹

For patients with genotype 1a with cirrhosis, the recommended duration of treatment with *Viekira Pak* plus ribavirin is 24 weeks. There is the potential to reduce the duration to 12 weeks in some patients, depending on their treatment history.¹ The results of the TURQUOISE-II study showed that patients who were naive to treatment had similar rates of SVR12 whether randomized to 12 weeks (92.2%) or 24 weeks of treatment (95%). Among patients who were prior null responders with peginterferon therapy, an SVR12 was achieved in 80% of patients after 12 weeks of therapy and 93% of patients after 24 weeks of therapy. Among those with a prior partial response to peginterferon therapy, an SVR12 was achieved in 100% of patients with both treatment durations. Among those who had experienced relapse

with peginterferon therapy, an SVR12 was achieved in 93% of patients after 12 weeks of therapy and 100% after 24 weeks of therapy.^{1,28}

For patients with genotype 1b without cirrhosis, the recommended duration of treatment with *Viekira Pak* is 12 weeks; patients with cirrhosis should be treated with a combination of *Viekira Pak* plus ribavirin for 12 weeks.¹

In patients with mixed or unknown genotype 1 subtype, the dosing schedule for the treatment of genotype 1a is recommended.¹

In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir score of 2 or lower), the recommended treatment is *Viekira Pak* plus ribavirin for 24 weeks, regardless of subtype. If the patient is being treated with a calcineurin inhibitor (eg, cyclosporine, tacrolimus), the dose of the calcineurin inhibitor may need to be adjusted.¹

Table 5 summarizes the recommended treatment durations for the available regimens by genotype and presence/absence of cirrhosis.¹⁻⁵

No dosage adjustments are necessary for patients with mild hepatic impairment. The use of *Viekira Pak* in patients with moderate hepatic impairment (Child-Pugh class B) is not recommended; use is contraindicated in those with severe hepatic impairment (Child-Pugh class C).¹ No dosing adjustments are recommended for patients with renal impairment.¹

In patients coinfecting with HCV/HIV-1 treated with *Viekira Pak* plus ribavirin and either atazanavir- or raltegravir-based antiretroviral therapy for 12 weeks, SVR12 was seen in 93.8% and 93.3% of patients, respectively.²⁷

Table 5. Treatment duration of direct-acting antivirals for hepatitis C virus genotype 1¹⁻⁵

Agent	HCV genotype 1 without cirrhosis	HCV genotype 1a without cirrhosis as a component of combination therapy with ribavirin	HCV genotype 1a with cirrhosis as a component of combination therapy with ribavirin	HCV with cirrhosis	HCV genotype 1b without cirrhosis	HCV genotype 1b with cirrhosis as a component of combination therapy with ribavirin	HCV genotype 1
<i>Viekira Pak</i>		12 weeks	24 weeks		12 weeks	12 weeks	
Boceprevir plus peginterferon-alfa plus ribavirin; previous null responders	49 weeks						

(continued)

Table 5. Treatment duration of direct-acting antivirals for hepatitis C virus genotype 1¹⁻⁵ (CONT.)

Agent	HCV genotype 1 without cirrhosis	HCV genotype 1a without cirrhosis as a component of combination therapy with ribavirin	HCV genotype 1a with cirrhosis as a component of combination therapy with ribavirin	HCV with cirrhosis	HCV genotype 1b without cirrhosis	HCV genotype 1b with cirrhosis as a component of combination therapy with ribavirin	HCV genotype 1
Boceprevir plus peginterferon-alfa plus ribavirin; previous partial responders or relapsers	36 to 48 weeks						
Boceprevir plus peginterferon-alfa plus ribavirin; treatment-naïve patients	28 to 48 weeks; response-guided duration			4 weeks of peginterferon-alfa and ribavirin, then 44 weeks of boceprevir			
Ledipasvir/sofosbuvir; treatment-naïve patients	12 weeks			12 weeks			
Ledipasvir/sofosbuvir; treatment-experienced patients	12 weeks			24 weeks			
Simeprevir plus peginterferon-alfa plus ribavirin; prior nonresponders	12 weeks combination therapy, followed by 36 weeks of peginterferon-alfa plus ribavirin						
Simeprevir plus peginterferon-alfa plus ribavirin; treatment-naïve patients and prior relapsers	12 weeks combination therapy, followed by 12 weeks of peginterferon-alfa plus ribavirin						
Simeprevir plus sofosbuvir; treatment-experienced patients	12 weeks			24 weeks			
Simeprevir plus sofosbuvir; treatment-naïve patients	12 weeks			24 weeks			
Sofosbuvir plus peginterferon-alfa plus ribavirin							12 weeks

PRODUCT AVAILABILITY

Viekira Pak was approved by the US Food and Drug Administration on December 19, 2014.³³ It is supplied as a 28-day carton containing 4 weekly cartons of 7 daily dose packs. Each daily dose contains 4 tablets: 2 coformulated ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg tablets and 2 dasabuvir 250 mg tablets. The daily dose pack indicates which tablets are to be taken in the morning and which are to be taken in the evening. Store at or below 86°F (30°C) and away from children.¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for *Viekira Pak*.

CONCLUSION

Viekira Pak is the second all oral combination therapy approved for the treatment of chronic HCV infection. Rates of SVR12 in clinical trials were higher than historical controls and similar to other all-oral treatment options. Durability of treatment is limited to 1 open-label trial of various combinations of the components of *Viekira Pak*. Only 2 studies reported SVR beyond 12 weeks. Most of the published literature describes studies with long-term follow-up periods, but the long-term follow-up results have yet to be reported. Adverse events are typical of ribavirin and include fatigue, nausea, and decreased hemoglobin. Multiple drug-drug interactions and twice-daily dosing may complicate therapy. Significant monitoring before, during, and after therapy is required to ensure adequate safety and efficacy.

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