New combination antiviral for the treatment of hepatitis C

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Purpose. The pharmacology, pharmacokinetics, clinical efficacy, and safety of Viekira, as well as its place in hepatitis C virus (HCV) therapy, are reviewed.

Summary. Ombitasvir 25 mg–paritaprevir 150 mg–ritonavir 100 mg plus dasabuvir 250 mg (Viekira) is approved in the United States as a combination direct-acting antiviral agent for treatment-naive or treatment-experienced patients with HCV genotype 1 infection, including those with compensated cirrhosis. It is the first coformulated direct-acting antiviral that targets different stages of the virus’s life cycle. Viekira is administered as an oral, interferon-free regimen. Phase III clinical trials demonstrated that Viekira administered with or without ribavirin can achieve sustained virological response rates of ≥90%. These results are notable because they show that high virological cure rates can be achieved without peginterferon and ribavirin. Viekira is also effective for special patient populations, such as individuals coinfected with HIV, liver transplant recipients, and those with advanced renal disease. The most frequently reported adverse effects among patients associated with Viekira without ribavirin were nausea, pruritus, and insomnia. During clinical trials, the most common adverse effects among patients receiving Viekira with ribavirin were fatigue, nausea, pruritus, insomnia, and weakness.

Conclusion. Viekira, the first coformulated direct-acting antiviral that targets different stages of the HCV life cycle, is an interferon-free treatment for HCV genotype 1 infection. It is associated with a virological cure rate of ≥90% and treatment durations of 12 and 24 weeks. Viekira is also effective and safe for patients who have undergone liver transplantation, are coinfected with HIV, or have advanced kidney disease.

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There are seven hepatitis C virus (HCV) genotypes with marked differences in global geographic distribution.1 While different genotypes express minimal overall differences in disease progression, they exhibit clear differences in susceptibility to antiviral therapy. HCV genotype 1 is predominantly found in the United States, comprising 70–80% of HCV infections, followed by HCV genotypes 2, 3, and 4 in the order of prevalence.2 Before the advent of second-generation direct-acting antivirals, HCV genotype 1 infections were the most difficult to eradicate in the United States. HCV genotype 1 encompasses 11 subgenotypes, with genotypes 1a, 1b, and 1c causing the majority of infections.3

Before the emergence of direct-acting antiviral agents, peginterferon alfa–ribavirin therapy was the standard of care for HCV infection. For over a decade, the use of peginterferon alfa–ribavirin therapy resulted in relatively poor sustained virological response (SVR) rates, ranging from 40% to 50% for genotype 1 infections.4,5 SVR is defined as an undetectable HCV level in the blood during treatment and for 12 weeks after treatment completion.6 SVR, a key response measure for treatment effectiveness, is associated with decreases in all-cause mortality, liver-related death.
rates and complications, and hepatocellular cancer rates.7,8 Peginterferon alfa–ribavirin therapy is also noted to cause intolerable adverse effects and high rates of viral relapse.5,9

The approval of the first-generation HCV protease inhibitors, boceprevir and telaprevir, marked a major breakthrough toward achieving higher SVR rates when used in combination with peginterferon alfa–ribavirin compared with peginterferon alfa–ribavirin therapy alone for patients with HCV genotype 1 infection. Both drugs inhibited the nonstructural protein 3/4A serine protease enzyme complex and were used as adjunctive therapy with peginterferon alfa–ribavirin. SVR rates varied from 70% to 80% when treatment-naive patients were taking either boceprevir or telaprevir with peginterferon alfa–ribavirin.10–12 However, their use was hampered by a cumbersome response-guided therapy approach, an increased pill burden, drug–drug interactions, low barriers to resistance, and notable adverse effects.13–16

More recently, newer-generation HCV direct-acting antivirals, consisting of protease inhibitors, nonstructural protein inhibitors, and RNA polymerase inhibitors, have demonstrated better pharmacologic properties, clinical efficacy, and safety profiles.

Oral, interferon-free ombitasvir–paritaprevir–ritonavir plus dasabuvir (Viekira Pak, AbbVie) was approved by the Food and Drug Administration (FDA) on December 19, 2014, for the treatment of HCV genotype 1 infected persons (treatment naïve and treatment experienced), including those with compensated cirrhosis. Viekira is a standalone, fixed-dose combination regimen administered with or without ribavirin, depending on the patient’s HCV subtype, cirrhosis status, and treatment experience.17 It is the fourth agent of the newer generation of direct-acting antivirals available for patients infected with HCV genotype 1 and coinfected with human immunodeficiency virus (HIV). Viekira is currently not recommended in patients with decompensated cirrhosis.17,18 This article reviews the pharmacology, pharmacokinetics, clinical efficacy, and safety of Viekira, as well as its place in HCV therapy.

Background

HCV is prolific and produces up to 10^{10} particles daily.19 It has an enveloped, positive-sense, single-stranded RNA genetic material of approximately 9600 base pairs in length. Once inside the hepatocyte, the viral genome is released from the nucleocapsid, and the HCV polyprotein is translated via the internal ribosome. The polyprotein is cleaved by cellular and viral proteases to yield structural and nonstructural proteins.20 The core nonstructural 3 and 5A proteins form the replication complex on lipid droplets and serve as a scaffold for the RNA polymerase to replicate the viral genome. Its genome encodes a single long polyprotein that is processed into 10 separate proteins by viral enzymes (nonstructural proteins) and cellular enzymes (structural proteins).21 There are 4 major structural proteins and at least 6 nonstructural proteins that comprise the protease, helicase, and RNA-dependent RNA polymerase activities of the virus.20–22 The HCV nonstructural proteins comprise the RNA replication machinery (Figure 1).23

Every step in viral replication is considered a potential drug target, including RNA genome translation, assembly, and export of progeny viruses. The direct-acting antivirals include nonstructural 3/4A serine protease inhibitors, nucleoside–nucleotide and nonnucleoside inhibitors of the nonstructural 5B polymerase, and nonstructural 5A inhibitors.24–25 These drugs primarily target the replication, polyprotein processing, packaging in nucleocapsid, assembly, and release of HCV infectious particles. The plus-stranded viral RNA is first translated into a large polyprotein that is then cleaved by host and viral proteases into structural and enzymatic proteins, respectively.26 The small, error-prone, RNA-dependent RNA polymerase is a major transcription factor, accounting for the high mutability and rapid acquisition of resistance because it lacks proofreading ability. This genetic characteristic contributes to the virus’s genetic diversity.19

Pharmacology

The components of Viekira target three different protein enzymes that are essential for the HCV life cycle. Ombitasvir inhibits the HCV nonstructural 5A protein complex, which is required for viral replication and assembly. Similarly, dasabuvir inhibits the HCV nonstructural 5B RNA-dependent RNA polymerase, which suppresses viral replication. Paritaprevir works at a later stage of the virus’s life cycle and inhibits the nonstructural 3/4A serine protease, which is required for proteolytic cleavage of the HCV-encoded polyprotein leading to mature viruses.27 In addition, inhibition of the protease may promote innate immune signaling, which may help with viral clearance.

Ritonavir, a HIV protease inhibitor and a potent cytochrome P-450 (CYP) isozyme 3A4 inhibitor, is formulated with paritaprevir as a pharmacokinetic enhancer to increase the plasma concentrations and half-life of paritaprevir, thus allowing for once-daily dosing.17 Ritonavir does not have any activity against HCV. The dosage and oral administration of Viekira are two tablets of fixed-dose combination ombitasvir 12.5 mg–paritaprevir 75 mg–ritonavir

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**KEY POINTS**

- Viekira could be used in patients infected with HCV who have advanced renal impairment.
- Viekira is contraindicated for use in patients with Child–Pugh class cirrhosis.
- Viekira could be used for HCV-HIV coinfected patients.
The regimen should be administered with a meal. The steady-state maximum plasma concentrations for ombitasvir, paritaprevir, ritonavir, and dasabuvir are well absorbed within four to five hours after oral ingestion. Relative to fasting conditions, a moderately fatty meal (approximately 600 calories, 20–30% from fat) increases the mean area under the concentration–time curve (AUC) of ombitasvir, paritaprevir, ritonavir, and dasabuvir to 82%, 211%, 49%, and 30%, respectively. The administration of a high-fat meal (900 calories, 60% from fat) increases the mean AUC of ombitasvir, paritaprevir, ritonavir, and dasabuvir by 76%, 180%, 44%, and 22%, respectively. Therefore, the regimen should be administered with a meal. The mean elimination half-life of ombitasvir is approximately 21–25 hours. The mean plasma half-lives of paritaprevir and dasabuvir are approximately 5.5 and 5.5–6 hours, respectively. The mean plasma half-life of ritonavir is approximately 4 hours after its administration with ombitasvir and paritaprevir.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir are highly bound to human plasma proteins (99.9%, 98.6%, 99.0%, and 99.5%, respectively). Ombitasvir is primarily metabolized by amide hydrolysis followed by oxidative metabolism. In contrast, paritaprevir and ritonavir are predominantly metabolized by CYP3A4. Dasabuvir is primarily metabolized by CYP2C8. The mean elimination half-life of ombitasvir is approximately 21–25 hours. The mean plasma half-lives of paritaprevir and dasabuvir are approximately 5.5 and 5.5–6 hours, respectively. The mean plasma half-life of ritonavir is approximately 4 hours after its administration with ombitasvir and paritaprevir.
The AUC values are notably affected by the severity of liver disease, suggesting the regimen should not be recommended for HCV-infected individuals with moderate hepatic impairment (Child-Pugh class B). Furthermore, the combination regimen is contraindicated in patients with severe hepatic impairment (Child-Pugh class C) due to the risk of accumulation and toxicity.29,30 In vivo data suggest that the changes in exposure to ombitasvir, paritaprevir, ritonavir, and dasabuvir in subjects with mild (creatinine clearance [CLcr], 60–89 mL/min), moderate (CLcr, 30–59 mL/min), and severe (CLcr, 15–29 mL/min) renal impairment are not clinically notable.29,32 Thus, no dosage adjustments are recommended for Viekira in patients with mild-to-severe renal impairment. No pharmacokinetic data are available for ombitasvir, paritaprevir, ritonavir, and dasabuvir in non-HCV-infected subjects with end-stage renal disease.

Clinical efficacy

The efficacy of Viekira with or without ribavirin was evaluated in six pivotal Phase III, randomized, multicenter trials—PEARL-II, PEARL-III, PEARL-IV, SAPPHIRE-I, SAPPHIRE-II, and TURQUOISE-II.33-37 The trials enrolled more than 2300 patients with HCV genotype 1 infection with or without cirrhosis. Study patients were randomly assigned to receive Viekira or placebo with or without ribavirin for 12 or 24 weeks. Ribavirin was dosed according to body weight (<75 kg = 1000 mg/day; ≥75 kg = 1200 mg/day). Viekira was also evaluated in special populations comprised of genotype 1 infected patients with liver transplantation, coinfected with HIV, or with advanced renal disease. The primary efficacy endpoint for the clinical trials was SVR rates 12 weeks after treatment completion, or virological cure.

PEARL-II. PEARL-II was an open-label trial that evaluated the efficacy of Viekira in 186 patients without cirrhosis with HCV genotype 1b whose disease had relapsed, partially responded, or did not respond to previous treatment with peginterferon–ribavirin therapy.31 Patients were stratified by prior response to peginterferon alfa–ribavirin (relapse, partial response, or null response) and randomized in a 1:1 ratio to receive Viekira with (n = 91) or without (n = 95) ribavirin for 12 weeks. The mean SVR rate was 100% for patients who did not receive ribavirin, compared with 97% in the group receiving ribavirin. No virological failures were reported. Viekira was well tolerated, with only 2 people in the ribavirin-containing group discontinuing treatment early due to adverse events. Results from this study demonstrated that patients with genotype 1b who did not respond to peginterferon alfa–ribavirin therapy can achieve very high cure rates with an oral peginterferon alfa-free regimen without ribavirin.

PEARL-III and PEARL-IV. The PEARL-III and PEARL-IV trials were similar in design.34 These double-blind, placebo-controlled trials evaluated the efficacy of Viekira, with or without ribavirin, for 12 weeks in treatment-naive patients without cirrhosis. Patients were randomized to receive either ribavirin or matching placebo; all patients received open-label Viekira. Patients in both trials who received Viekira plus ribavirin achieved significantly higher SVR rates compared with patients who did not receive ribavirin. The only major difference between the two studies was that PEARL-III enrolled patients with HCV genotype 1b (n = 419) and PEARL-IV enrolled patients with HCV genotype 1a (n = 305). The majority of patients in both trials had mild-to-moderate liver fibrosis (stage F0–F2). Among patients with HCV genotype 1b (PEARL-III), 99.0% (ribavirin-free group) and 99.5% (ribavirin-treated group) achieved an SVR. Only 1 patient in the ribavirin-free group experienced virological failure.

Similarly, among patients with HCV genotype 1a (PEARL-IV), 90.2% (ribavirin-free group) and 97.0% (ribavirin-treated group) achieved an SVR.34 The difference in cure rates between the two groups was attributed to the greater number of virological failures experienced by patients not receiving ribavirin compared with those in the ribavirin-treated group (7.8% versus 2.0%). Eighteen patients with HCV genotype 1a had virological failure, 16 of whom were in the group not receiving ribavirin. Thus, the use of ribavirin in patients with HCV genotype 1a may confer additional benefit. The patients who experienced treatment failure had at least one amino acid variant that conferred resistance to one of the three components of the regimen.

SAPPHIRE-I. SAPPHIRE-I was a double-blind, placebo-controlled trial that enrolled 631 treatment-naive patients with HCV genotype 1 infection without cirrhosis.35 Patients were randomized in a 3:1 ratio to receive Viekira with ribavirin (n = 473) or matching placebo (n = 158) for 12 weeks. Patients were stratified by HCV subtype (genotype 1a versus genotype 1b). After 12 weeks of the blinded study phase, the placebo group received Viekira with ribavirin for an additional 12 weeks (open-label treatment period). The SVR rates were slightly higher for patients with HCV genotype 1b compared with HCV genotype 1a (98% versus 95.3%, respectively). The overall SVR rate was 96.2% at 12 weeks after treatment completion (95% confidence interval [CI], 94.5–97.9%). The discontinuation rate due to adverse events was 0.6% in both groups. Eight patients with genotype 1a infection had at least one amino acid variant that conferred resistance to one of the three components of the regimen.
One patient had virological failure during treatment (0.2%), and 7 patients relapsed by posttreatment week 12 (1.5%). Data from SAPPHIRE-I reinforced the findings from the PEARL-III and PEARL-IV trials, showing that high SVR rates can be achieved with a 12-week treatment course of Viekira with ribavirin, especially for treatment-naive, noncirrhotic patients with HCV genotype 1a infection.

SAPPHIRE-II. SAPPHIRE-II mirrored SAPPHIRE-I in study design. However, SAPPHIRE-II enrolled treatment-experienced, noncirrhotic patients with HCV genotype 1 infection (n = 394).^{25} Patients were stratified by HCV subtype (genotype 1a versus genotype 1b) and prior response to peginterferon alfa–ribavirin therapy (relapse, partial response, or null response). Patients were randomly assigned in a 3:1 ratio to receive Viekira with ribavirin (n = 297) or matching placebo (n = 97) during a 12-week double-blind period. After 12 weeks of the blinded study phase, the placebo group received Viekira with ribavirin for 12 weeks (open-label treatment period). SVR rates were similar for patients with HCV genotype 1a and 1b infections (96.0% and 96.7%, respectively). Response rates were further evaluated based on patients’ prior response to peginterferon–ribavirin (relapse [95.3%], partial response [100%], and null response [95.2%]). Seven patients (2.4%) experienced posttreatment relapse, 4 of whom had HCV genotype 1a; 1 patient had HCV genotype 1b. Relapse was associated with at least one amino acid variant that conferred resistance to one of the three components of the regimen. Three patients in the treatment group (1.0%) discontinued the regimen due to adverse events, such as elevated transaminase levels (grade 3), diarrhea, and acute renal failure (unrelated to the Viekira regimen). The overall mean SVR rate was 96.3% (95% CI, 94.2–98.4%). The findings from SAPPHIRE-II suggested that a 12-week course of Viekira plus ribavirin was effective for treatment-experienced, noncirrhotic patients with HCV genotype 1, regardless of previous treatment failure with peginterferon alfa–ribavirin.

TURQUOISE-II. TURQUOISE-II was an open-label study that evaluated the efficacy of Viekira with ribavirin in 380 treatment-naive and treatment-experienced patients with HCV genotype 1 who had compensated cirrhosis (Child–Pugh class A).^{37} Patients were randomized in a 1:1 ratio to receive treatment for 12 weeks (n = 208) or 24 weeks (n = 172). Treatment-naive and treatment-experienced patients were stratified by HCV subtype (genotype 1a versus genotype 1b). Treatment-experienced patients were further stratified based on their prior response to peginterferon alfa–ribavirin (relapse, partial response, or null response). Results showed that 191 patients in the 12-week group and 165 patients in the 24-week group achieved similar SVR rates (91.8% and 95.9%, respectively; p = 0.09). Thirteen patients (6.2%) in the 12-week group had virological failure during the study or relapsed after treatment, compared with 4 patients (2.3%) in the 24-week group. Altogether, 12-week and 24-week treatment with Viekira plus ribavirin resulted in high SVR rates in patients with HCV genotype 1 and cirrhosis.

TURQUOISE-I. Viekira was also studied in special patient populations with HIV and HCV coinfection, who had undergone liver transplantation, and with advanced renal disease.^{40} FDA approval of Viekira for HIV–HCV coinfected persons was based on the TURQUOISE-I trial. This Phase II/III, randomized, open-label, uncontrolled study evaluated the efficacy and safety of Viekira with ribavirin for 12 or 24 weeks. Study enrollment included 63 HIV patients coinfected with HCV genotype 1 who were HCV treatment naive or treatment experienced with peginterferon alfa–ribavirin. Nineteen percent of patients had compensated cirrhosis (Child–Pugh class A). Enrolled patients’ HIV infection was stabilized with atazanavir-based or raltegravir-based antiretroviral regimens. For patients receiving ritonavir-boosted atazanavir, the ritonavir component was discontinued while they received Viekira with ribavirin. Atazanavir was administered with the morning dose of Viekira and ribavirin. The ritonavir component of the antiretroviral regimen was resumed after HCV therapy was completed. The SVR rates were similar for patients in the 12- and 24-week groups (94% and 91%, respectively; p > 0.99). Hence, treatment with Viekira plus ribavirin resulted in high SVR rates among patients coinfected with HCV genotype 1 and HIV.

CORAL-1. The efficacy and safety of Viekira were also studied in liver transplant recipients.^{41} CORAL-1, a Phase II, open-label, single-group study, evaluated Viekira with ribavirin for 24 weeks. It enrolled 34 liver transplant patients (at least 12 months posttransplantation) who had HCV genotype 1 infection, normal hepatic function, and a fibrosis score of ≤2. Low-dose ribavirin (600–800 mg/day) was administered at the discretion of the study investigators. Patients received immunosuppressants (taclorimus or cyclosporine with dosage modified by testing trough levels of calcineurin inhibitors) during treatment with Viekira. A SVR was achieved in 33 (97%) of 34 patients.

RUBY-1. The safety and efficacy of a 12- or 24-week course of Viekira, with or without ribavirin, were also evaluated in patients with chronic kidney disease.^{32} RUBY-1, a Phase IIIb, randomized, open-label trial, enrolled 20 treatment-naive, noncirrhotic patients with HCV genotype 1 infection and advanced renal disease (stage 4 or 5). Sixty-five percent of patients were receiving hemodialysis. Patients with HCV genotype 1a received Viekira with low-dose ribavirin (200 mg/day), while those with HCV genotype 1b received only Viekira. Patients undergoing hemodialysis received ribavirin four hours before each hemodialysis session. A SVR was achieved in 10 of 10 patients at the time of an interim analysis (posttreatment week 4).
**Drug resistance**

A pooled analysis of over 2500 patients treated with Viekira, with or without ribavirin, in Phase Ib and III clinical trials revealed that 3% of patients (n = 74) who experienced virological failure had treatment-emergent resistance, primarily post-treatment relapse.33-36,39 Among 67 patients with HCV genotype 1, 50 had nonstructural 3 variants, 46 patients had nonstructural 5A variants, and 37 had nonstructural 5B variants. Treatment-emergent variants were observed in all three viral targets for 30 patients. In contrast, among 7 patients with HCV genotype 1b, 4 had nonstructural 3 variants, 2 had nonstructural 5A variants, and 1 had both nonstructural 3 and 5A variants. There were no patients with HCV genotype 1b who developed resistant variants in all three viral targets. The common variants reported were D168V and R155K (nonstructural 3/4A), M28T and Q30R (nonstructural 5A), and S556G (nonstructural 5B).42-43 Currently, for patients who develop virological failure and resistance when treated with Viekira, the impact on subsequent therapy with other nonstructural 3/4A, nonstructural 5A, or nonstructural 5B inhibitors remains unknown.

**Drug–drug interactions**

Drug–drug interactions are anticipated with Viekira, as paritaprevir and ritonavir are predominantly CYP3A4 substrates. Coadministration with either potent CYP3A4 inducers or inhibitors will notably reduce or increase the plasma concentrations of paritaprevir and ritonavir, respectively. Dasabuvir is predominantly a CYP2C8 substrate. When coadministered with CYP2C8 inhibitors, plasma dasabuvir concentrations will appreciably increase.31,44 On the other hand, coadministration of paritaprevir, ritonavir, and dasabuvir with potent CYP2C8 inducers may reduce plasma concentrations of paritaprevir, ritonavir, and dasabuvir. Ombitasvir, paritaprevir, ritonavir, and dasabuvir are substrates of the P-glycoprotein transporter. In addition, ombitasvir, paritaprevir, and dasabuvir are substrates of the breast cancer resistance protein (BCRP) transporter. Paritaprevir is a substrate of membrane transport proteins called organic anion-transporting polypeptides (OATP) B1 and B3.44,45 Therefore, coadministration with inhibitors of P-glycoprotein, BCRP OATP1B1 or OATP1B3 may increase the plasma concentrations of the individual components of the regimen. Aside from being metabolized via hydrolysis, oxidation, or CYP450 enzymes, ombitasvir, paritaprevir, ritonavir, and dasabuvir are also inhibitors of various transporters and CYP3A4. Ombitasvir, paritaprevir, and dasabuvir are inhibitors of uridine diphosphate glucuronosyltransferase 1 polypeptide A1. Paritaprevir, dasabuvir, and ritonavir also inhibit BCRP. Furthermore, paritaprevir inhibits OATP1B1 and OATP1B3.44,45 Ritonavir is also a potent inhibitor of CYP3A4. In summary, coadministration of Viekira is contraindicated with drugs that are (1) potent CYP3A or CYP2C8 inducers, (2) potent CYP2C8 inhibitors, or (3) highly dependent on CYP3A for clearance.

Coadministration of Viekira with HIV antiretrovirals such as darunavir–ritonavir, lopinavir–ritonavir, and rilpivirine is not recommended.46 When Viekira is coadministered with an HIV regimen containing atazanavir, atazanavir should be taken in the morning without additional ritonavir. Coadministration with drug classes such as antifungals, immunosuppressants (cyclosporine, tacrolimus), particular hydroxyethylthiouracil–coenzyme A reductase inhibitors (rosuvastatin, pravastatin), omeprazole, or salmeterol requires close monitoring and dosage adjustments.44 When Viekira is coadministered with ribavirin, the warnings, precautions, and contraindications to ribavirin also apply. Table 1 summarizes the drugs that are contraindicated with Viekira coadministration.

**Safety and tolerability**

Treatment with Viekira is generally safe and well tolerated.27,28 The most frequently reported adverse effects (≥5% of patients) associated with Viekira without ribavirin were nausea, pruritus, and insomnia.33-36,48 During clinical trials, the most common adverse effects (≥10%) among patients receiving Viekira with ribavirin were fatigue, nausea, pruritus, insomnia, and weakness.33-37,40 Temporary mild-to-moderate anemia was more commonly associated with ribavirin as an adverse effect; reductions in the dosage of ribavirin may help alleviate adverse effects associated with anemia.40 Mild, self-limiting, rash-related events were also reported during the trials, especially in patients treated with ribavirin-containing regimens.33-36,49 No serious cutaneous reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, or drug rash with eosinophilia and systemic symptoms, were reported.

**Place in therapy**

Viekira is approved only for the treatment of HCV genotype 1 infection in the United States. It is coadministered with ribavirin for patients infected with HCV genotype 1a, with or without compensated cirrhosis, and for patients with HCV genotype 1b with compensated cirrhosis. Viekira can be administered without ribavirin for patients with HCV genotype 1b who do not have cirrhosis. It is not recommended for patients who have not responded to (1) triple therapy with peginterferon alfa–ribavirin plus an HCV protease inhibitor or (2) a sofosbuvir-containing regimen.48 More importantly, Viekira is effective and safe for patients who have undergone liver transplantation, are coinfected with HIV, or have advanced kidney disease. Table 2 illustrates the recommended Viekira regimens for patients with HCV genotype 1 infection, with HIV coinfection, and who have undergone liver transplantation. Close monitoring of drug–drug interactions is important as Viekira is coadministered with an HIV protease inhibitor. When Viekira is coadministered with a potent CYP3A4 inhibitor, the dosage of CYP3A4 substrates should be adjusted. The other drugs should be added only if the benefits outweigh the risks. When Viekira is coadministered with a potent CYP3A4 inducer, the dosage of CYP3A4 substrates should be reduced. The other drugs should be added only if the benefits outweigh the risks.
### Table 1. Drugs Contraindicated With Viekira Coadministration

<table>
<thead>
<tr>
<th>Contraindicated Drug(s)</th>
<th>Adverse Effect(s)</th>
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<tbody>
<tr>
<td>Alfuzosin</td>
<td>Risk of hypotension</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Potent inductive effects by this anticonvulsant will significantly reduce plasma levels of ombitasvir, paritaprevir, ritonavir, and dasabuvir, resulting in loss of therapeutic efficacy</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>Coadministration of ergot derivatives with ritonavir, a potent inhibitor, may result in significantly increased plasma ergot levels, resulting in acute ergot toxicity characterized by vasoconstriction and tissue ischemia</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Efavirenz is a potent CYP3A inducer; coadministration of efavirenz-based regimens with paritaprevir and ritonavir plus dasabuvir was poorly tolerated and led to increased liver enzymes</td>
</tr>
<tr>
<td>Ergonovine</td>
<td>Coadministration of ergot derivatives with ritonavir, a potent inhibitor, may result in significantly increased plasma ergot levels, resulting in acute ergot toxicity characterized by vasoconstriction and tissue ischemia</td>
</tr>
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</tr>
<tr>
<td>Gemfibrozil</td>
<td>Inhibition of CYP2C8 by gemfibrozil increases dasabuvir levels by 10-fold, which may result in risk of Q-T interval prolongation</td>
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<tr>
<td>Lovastatin</td>
<td>Risk for myopathy including rhabdomyolysis due to inhibition by Viekira</td>
</tr>
<tr>
<td>Methyl/ergonovine</td>
<td>Coadministration of ergot derivatives with ritonavir, a potent inhibitor, may result in significantly increased plasma ergot levels, resulting in acute ergot toxicity characterized by vasoconstriction and tissue ischemia</td>
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<tr>
<td>Midazolam (oral)</td>
<td>Risk for significant increases in plasma midazolam levels due to inhibition by Viekira; could result in prolonged sedation or respiratory depression</td>
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<tr>
<td>Oral contraceptives</td>
<td>Risk of ALT elevations; FDA recommends that women use alternative contraceptive methods during Viekira therapy</td>
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<tr>
<td>Phenytoin</td>
<td>Potent inductive effects by this anticonvulsant will significantly reduce plasma levels of ombitasvir, paritaprevir, ritonavir, and dasabuvir, resulting in loss of therapeutic efficacy</td>
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<tr>
<td>Pimozide</td>
<td>Risk for cardiac arrhythmias due to inhibition by Viekira</td>
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<tr>
<td>Rifampin</td>
<td>Potent inductive effects by rifampin will significantly reduce plasma levels of ombitasvir, paritaprevir, ritonavir, and dasabuvir, resulting in loss of therapeutic efficacy</td>
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<tr>
<td>Sildenafil</td>
<td>Risk for increased sildenafil-associated adverse events including visual disturbances, hypotension, priapism, and syncope due to inhibition by Viekira</td>
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<tr>
<td>Simvastatin</td>
<td>Risk for myopathy including rhabdomyolysis due to inhibition by Viekira</td>
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<tr>
<td>St. John’s wort (<em>Hypericum perforatum</em>)</td>
<td>Coadministration with St. John’s wort (CYP3A inducer) may result in significantly decreased plasma levels of ombitasvir, paritaprevir, ritonavir, and dasabuvir, resulting in loss of therapeutic efficacy</td>
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<tr>
<td>Triazolam</td>
<td>Risk for significant increases in plasma triazolam levels due to inhibition by Viekira; could result in prolonged sedation or respiratory depression</td>
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</table>

*CYP = cytochrome P-450 isozyme, ALT = alanine transaminase, FDA = Food and Drug Administration.

### Conclusion

Viekira, the first coformulated direct-acting antiviral that targets different stages of the HCV life cycle, is an interferon-free treatment for HCV genotype 1 infection. It is associated with a virological cure rate of ≥90% and treatment durations of 12 and 24 weeks. Viekira is also effective...
Table 2. Recommended Treatment Regimens for Viekira in Patients With HCV or HCV–HIV Coinfection16,40–41

<table>
<thead>
<tr>
<th>Patient Population*</th>
<th>Regimen</th>
<th>Treatment Duration (wk)</th>
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<tbody>
<tr>
<td>HCV genotype 1a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without cirrhosis</td>
<td>Viekira plus ribavirin</td>
<td>12</td>
</tr>
<tr>
<td>With cirrhosis</td>
<td>Viekira plus ribavirin</td>
<td>24a</td>
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<tr>
<td>HCV genotype 1b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without cirrhosis</td>
<td>Viekira only</td>
<td>12</td>
</tr>
<tr>
<td>With cirrhosis</td>
<td>Viekira plus ribavirin</td>
<td>12</td>
</tr>
<tr>
<td>Liver transplantation with normal hepatic function and mild fibrosis (META VIR fibrosis score of ≤2)</td>
<td>Viekira plus ribavirin</td>
<td>24c</td>
</tr>
</tbody>
</table>

*Population includes treatment-naive and treatment-experienced patients who did not respond to prior treatment with peginterferon–ribavirin. HCV = hepatitis C virus, HIV = human immunodeficiency virus.
*Viekira plus ribavirin for 12 weeks may be considered for treatment-naive patients or patients who had prior relapse or partial response to prior therapy with peginterferon-ribavirin.
*Treatment duration is 24 weeks, regardless of HCV genotype 1 subtype. Dosage adjustments are required with cyclosporine or tacrolimus due to drug interactions.41

and safe for patients who have undergone liver transplantation, are coinfected with HIV, or have advanced kidney disease.

Disclosures
The authors have declared no potential conflicts of interest.

References
28. Bernstein B, Menon RM, Klein CE et al. Pharmacokinetics and tolerability of the HCV protease inhibitor ABT-450 following single ascending doses in healthy adult volunteers with and without ritonavir. Paper presented at...
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