Hepatitis C Agents
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Mfr	FDA-Approved Indications
Interferons		
peginterferon alfa-2a (Pegasys®)[1]	Genentech	Chronic hepatitis C ▪ Treatment of adults with chronic hepatitis C as part of a combination regimen with other hepatitis C virus antiviral drugs in patients ≥ 5 years old with compensated liver disease ▪ Monotherapy is not recommended unless a patient has a contraindication to, or significant intolerance of, other HCV antiviral drugs Chronic hepatitis B ▪ Treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B in adults with compensated liver disease and evidence of viral replication and liver inflammation
peginterferon alfa-2b (PEGIntron®)[2]	Merck Sharp & Dohme	Chronic hepatitis C ▪ For patients with compensated liver disease in combination with ribavirin (Rebetol) and an approved Hepatitis C Virus (HCV) NS3/4A protease inhibitor in adult patients (≥18 years old) with HCV genotype 1 infection ▪ For patients with compensated liver disease in combination with ribavirin (Rebetol) in patients with genotypes other than genotype 1, pediatric patients (3-17 years of age), or in patients with genotype 1 infection where the use of an HCV NS3/4A protease inhibitor is not warranted based on tolerability, contraindications, or other clinical factors Monotherapy should only be used in the treatment of chronic hepatitis C in patients with compensated liver disease if there are contraindications to, or significant intolerance of, ribavirin and is indicated for use only in previously untreated adult patients; Combination therapy provides substantially better response rates than monotherapy

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FDA-Approved Indications (continued)

Drug	Mfr	FDA-Approved Indications
Ribavirin		
ribavirin (Copegus®)[3]	generic, Genentech	Chronic hepatitis C ▪ In combination with peginterferon alfa-2a (Pegasys) in patients ≥ 5 years of age with compensated liver disease and have not been previously treated with interferon alfa ▪ Includes patients with histological evidence of cirrhosis (Child-Pugh A) ▪ Includes adult patients with clinically stable HIV disease and CD4 count > 100 cells/mm^2 Copegus must not be used as monotherapy; Safety and efficacy have not been demonstrated with treatment longer than 48 weeks; Safety and efficacy have not been established in liver or other organ transplant recipients, patients with decompensated liver disease, or previous non-responders to interferon therapy
ribavirin (Rebetol®)[4]	generic, Merck Sharp & Dohme	Chronic hepatitis C ▪ In combination with interferon alfa-2b (pegylated [PEG-Intron] or non pegylated [Intron-A®]) in patients (≥ 3 years of age) with compensated liver disease Rebetol must not be used as monotherapy; Combination therapy with ribavirin/peginterferon alfa-2b is preferred over ribavirin/interferon alfa-2b as this combination provides substantially better response rates; Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy: previous nonresponse, previous peginterferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection; No safety and efficacy data are available for treatment of longer than 1 year

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FDA-Approved Indications (continued)

Drug	Mfr	FDA-Approved Indications
Ribavirin (continued)		
ribavirin (Ribasphere®, Ribasphere RibaPak®)[5,6,7]	generic	Chronic hepatitis C Capsules ▪ In combination with interferon alfa 2b (pegylated and non pegylated) in patients ≥3 years of age with compensated liver disease Ribasphere must not be used as monotherapy; Combination therapy with ribavirin/peginterferon alfa-2b is preferred over ribavirin/interferon alfa-2b as this combination provides substantially better response rates; Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy: previous nonresponse, previous peginterferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection; No safety and efficacy data are available for treatment of longer than 1 year Tablets ▪ In combination with peginterferon alfa-2a (Pegasys) in adults with compensated liver disease and adults who have not been previously treated with interferon alpha ▪ Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh A) and patients with HIV disease that is clinically stable and CD4 count > 100 cells/mm^2 Safety and efficacy data are not available for treatment longer than 48 weeks; The safety and efficacy of ribavirin and peginterferon alfa-2a therapy have not been established in liver or other organ transplant recipients, patients with decompensated liver disease, or previous non-responders to interferon; Safety and efficacy have not been demonstrated for treatment longer than 48 weeks
ribavirin (Moderiba™)[8]	Abbvie	Chronic hepatitis C ▪ In combination with peginterferon alfa-2a for the treatment of adults with chronic hepatitis C (CHC) virus infection who have compensated liver disease and have not been previously treated with interferon alfa ▪ Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh A) and patients with HIV disease that is clinically stable and CD4 count > 100 cells/mm^3 Moderiba should not be used as monotherapy; Safety and efficacy data are not available for treatment longer than 48 weeks; The safety and efficacy of ribavirin and peginterferon alfa-2a therapy have not been established in liver or other organ transplant recipients, patients with decompensated liver disease, or previous non-responders to interferon

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FDA-Approved Indications (continued)

Drug	Mfr	FDA-Approved Indications
Oral Protease Inhibitors		
simeprevir (Olysio®)[9]	Janssen	Chronic hepatitis C genotype 1 or 4 infection ▪ As a component of a combination antiviral treatment regimen Simeprevir monotherapy is not recommended; When used in combination with peginterferon and ribavirin, screening patients with HCV genotype 1a infection for the presence of the NS3 Q80K polymorphism at baseline is strongly recommended as efficacy is substantially reduced in these patients and alternative therapy should be considered; Not recommended in patients who have previously failed therapy with a treatment regimen that included simeprevir (Olysio) or other HCV protease inhibitors;
Oral NS5A Inhibitor		
daclatasvir (Daklinza™)[10]	BMS	Chronic hepatitis C genotype 1 or 3 ▪ In combination with sofosbuvir with or without ribavirin Sustained virologic response (SVR) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving daclatasvir in combination with sofosbuvir for 12 weeks
Oral NS5B Polymerase Inhibitors		
sofosbuvir (Sovaldi®)[11]	Gilead	Chronic hepatitis C genotype 1, 2, 3, or 4 ▪ As a component of a combination antiviral treatment regimen
Oral Combination Products		
elbasvir/grazoprevir (Zepatier™)[12]	Merck	Chronic hepatitis C genotype 1 or 4 ▪ Co-formulated fixed dose tablet of elbasvir (an NS5A inhibitor) and grazoprevir (an NS3/4A protease inhibitor) ▪ Indicated for use with or without ribavirin ▪ Testing for NS5A resistance-associated polymorphisms needed for genotype 1a
ledipasvir/sofosbuvir (Harvoni®)[13]	Gilead	Chronic hepatitis C genotype 1, 4, 5, or 6 ▪ Co-formulated fixed dose tablet of ledipasvir (an NS5A inhibitor) and sofosbuvir (an NS5B Inhibitor) ▪ Indicated for use with or without ribavirin
ombitasvir/ paritaprevir/ritonavir + dasabuvir (Viekira Pak®, Viekira XR™)[14,15]	Abbvie	Chronic hepatitis C genotype 1 ▪ Viekira Pak and Viekira XR include the combination of ombitasvir (an NS5A inhibitor), paritaprevir (a protease inhibitor), ritonavir (a potent CYP3A inhibitor to pharmacologically boost paritaprevir), and dasabuvir (an NS5B polymerase inhibitor) ▪ Indicated for use with or without ribavirin, including in those with compensated cirrhosis
ombitasvir/ paritaprevir/ritonavir (Technivie®)[16]	Abbvie	Chronic hepatitis C genotype 4 ▪ Technivie includes the combination of ombitasvir (an NS5A inhibitor), paritaprevir (a protease inhibitor), and ritonavir (a potent CYP3A inhibitor to pharmacologically boost paritaprevir) ▪ Indicated for use in combination with ribavirin
sofosbuvir/velpatasvir (Epclusa)[17]	Gilead	Chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection ▪ Epclusa includes a combination of sofosbuvir (an NS5B polymerase inhibitor) and velpatasvir (an NS5A inhibitor) ▪ Indicated for use with or without ribavirin

Interferon alfacon -1 (Infergen®), an interferon product, and 2 oral protease inhibitors, boceprevir (Victrelis®) and telaprevir (Incivek®), are approved for use in the treatment of chronic hepatitis C but have been discontinued.

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OVERVIEW

Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States (U.S.). In approximately 15% to 25% of patients who become infected with hepatitis C, the virus is eliminated during the acute phase of the infection by T cell-mediated antiviral mechanisms; however, in the other 75% to 85% of patients, the HCV persists for decades.[18] Approximately 2.7 million people in the U.S. are chronically infected, although it is estimated that nearly 75% of these people may be unaware of their infection due to the insidious progression of the disease. HCV accounts for 40% of chronic liver disease in the U.S. In patients with chronic HCV infection followed for 20 years, disease progression to cirrhosis occurs in about 20% to 25%. Of those who develop cirrhosis, approximately 30% will develop end-stage liver disease over the next 10 years and 1% to 2% per year will develop hepatocellular carcinoma. HCV infection is the most common reason for liver transplantation and results in an estimated 8,000 to 10,000 deaths per year in the U.S.[19]

Transmission of HCV occurs primarily through percutaneous exposure to infected blood. The most important risk for HCV infection is injection-drug use, which accounts for at least 60% of acute HCV infections in the U.S. Other modes of transmission include mother-to-infant, receiving a blood or organ donation prior to 1992, occupational exposures, chronic hemodialysis, and contaminated devices shared for non-injection drug use, such as intranasal illicit drug use. Sexual transmission also occurs but generally seems to be inefficient except among HIV-infected men who have unprotected sex with men. Other risk factors include incarceration and receiving a tattoo in an unregulated setting. It is estimated that 29% of incarcerated persons in the North America are anti-HCV positive.[20]

Identification of persons infected with HCV is an important medical goal due to the proven benefits of care and treatment in reducing the risk of hepatocellular carcinoma and all-cause mortality. In addition, there is a potential public health benefit by reducing transmission through early treatment, viral clearance, and reduced risk behaviors.[21] The Centers for Disease Control and Prevention (CDC) estimates that baby boomers born from 1945 to 1965 account for 75% of all HCV infections. In August 2012, the CDC issued updated guidelines for HCV testing recommending all persons born from 1945 to 1965 (baby boomers) receive a 1-time testing for HCV without prior ascertaining risk-factor information.[22] In addition, both the CDC and the United States Preventive Services Task Force (USPSTF) recommend testing other persons based on exposures, behaviors, and conditions that increase the risk for HCV infection. Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV. In addition, all infected carriers of HCV should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions. [23]

Initial HCV testing is designed to detect the presence of HCV antibody (anti-HCV). The Food and Drug Administration (FDA)-approved tests include laboratory-based assays and a point-of-care assay that has a sensitivity and specificity similar to the FDA-approved laboratory-based HCV antibody assays. A positive test result for anti-HCV indicates the patient has a current active HCV infection (acute or chronic), the patient had a past infection that has resolved, or it is a false-positive test result. Therefore, a confirmatory test to detect the presence of HCV RNA is necessary prior to initiating treatment. Assays for HCV RNA are the most sensitive tests for HCV infection and represent the gold standard in establishing a diagnosis of HCV. HCV RNA is reported as international units (IUs) per milliliter; these quantitative assays allow detection of HCV RNA with a sensitivity as low as 5 IU/mL.

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HCV RNA can be detected within a few days of exposure to HCV, well before the presence of anti-HCV, and tends to persist for the duration of HCV infection.[24] Due to the diversity and the high mutation rate of HCV, immunity does not appear to develop after HCV infection. Testing of persons with suspected reinfection after previous spontaneous or treatment-related viral clearance should be done with initial HCV-RNA testing because an anti-HCV test is expected to be positive in this cohort of patients.[25] Prior to the initiation of HCV therapy, quantitative HCV RNA testing is also necessary to document the baseline level of viral load, as well as testing to determine the HCV genotype. Knowledge of the baseline viral load is utilized to measure the degree of viral decline after initiation of treatment; this is important for regimens requiring response-guided treatment decisions. Knowledge of the HCV genotype is important for selecting the most appropriate treatment regimen.

The standard measure of virological cure for hepatitis C treatment is the sustained virologic response (SVR).[26] SVR12 is defined as undetectable serum HCV RNA 12 weeks after discontinuation of treatment. When suppression of viral replication has been maintained for 12 weeks after treatment, the patient can be considered cured of chronic hepatitis C.[27] Prior to the approval of simeprevir (Olysio) and sofosbuvir (Sovaldi), all HCV therapies approved by the FDA had based efficacy assessment by the proportion of patients attaining SVR24 in the phase 3 confirmatory studies. However, SVR12 and SVR24 measurements have been found to be concordant, and SVR12 is now considered suitable as a primary endpoint for regulatory approval.[28]

There are 6 HCV genotypes and more than 50 subtypes. The distribution of HCV genotypes varies across the world. Genotype 1 is the most common worldwide and accounts for about 70 to 75% of U.S. infections; among African Americans, the frequency of genotype 1 is even higher at an estimated 90%.[29] In the U.S., genotype 1a and 1b represent about 75% and 25% of genotype 1 cases, respectively. Genotypes 2 and 3 account for the majority of the other approximate 25% to 30% HCV infections in the U.S. Genotype 4 predominates in Egypt, genotype 5 is localized to South Africa, and genotype 6 to Hong Kong and Southeast Asia.[30] Hepatitis C viral genotype is an important factor in selecting the optimal treatment planning, dictating drug selection, dose, and duration of treatment.

Historically, genotype 1 patients were treated with interferon monotherapy, which resulted in SVR rates of only 10% to 20%. With the addition of ribavirin, dual therapy of peginterferon + ribavirin (PEG/RBV) therapy achieved SVR rates of 40% to 50% in this genotype.[31] The first generation oral protease inhibitors, boceprevir (Victrelis) and telaprevir (Incivek), were introduced in 2011 representing the initial direct-acting antiviral agents (DAA) which act directly to disrupt the replication of the hepatitis C virus.[32] Their approval ushered in triple combination therapy consisting of an oral protease inhibitor, peginterferon, and ribavirin. Because of the triple combination therapy, improved rates of SVR for genotype 1 treatment-naïve patients of approximately 60% to 80% were reported.[33,34] Boceprevir (Victrelis) and telaprevir (Incivek) have since been discontinued. In 2013, simeprevir (Olysio) and sofosbuvir (Sovaldi) were approved. Simeprevir is a second-generation protease inhibitor approved for use in combination with sofosbuvir having an approximate SVR rate greater than 90% or for triple combination therapy with peginterferon and ribavirin associated with an approximate 80% SVR rate.[35] Sofosbuvir is the first in a new class of DAAs classified as an HCV nucleotide analog NS5B polymerase inhibitor approved in combination with peginterferon and ribavirin or with ribavirin alone, depending on the genotype. The combination of sofosbuvir with ribavirin was the first FDA-approved all-oral regimen for the treatment of HCV. By eliminating interferon, numerous adverse effects associated with interferon therapy are avoided. The resulting “all oral interferon-free” regimen is,

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therefore, more favorable. Beginning with sofosbuvir, and continuing with subsequently approved treatments, SVR rates as high as 90% or greater (depending on genotype and prior treatment experience) were demonstrated in clinical trials. In 2014, there were multiple rulings by the FDA that brought about new therapies for the treatment of hepatitis C and new indications for previously approved medications. In October 2014, the combination tablet of ledipasvir/sofosbuvir (Harvoni) received initial approval for genotype 1, and expanded approval in November 2015 for genotypes 4, 5, and 6. Ledipasvir is the first in a new class of DAAs classified as an HCV NS5A inhibitor available as a fixed dose combination with sofosbuvir taken as a single tablet once daily. In November 2014, simeprevir received FDA approval for use in combination with sofosbuvir. While this combination is not a co-formulated formulation, it does represent another all-oral treatment option. The combination ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak) was approved in December 2014 for use in genotype 1 with an extended release formulation (Viekira XR) approved in July 2016. This combination includes an NS5A inhibitor (ombitasvir), an NS3A/4A protease inhibitor (paritaprevir), a non-nucleoside NS5B polymerase inhibitor (dasabuvir), and a CYP3A inhibitor (ritonavir) to boost paritaprevir pharmacologically providing increased plasma concentrations. A similar combination, ombitasvir, paritaprevir, and ritonavir (Technivie), was approved in 2015 for the treatment of genotype 4 in combination with ribavirin. Daclatasvir (Daklinza), an NS5A inhibitor, was also approved in 2015. It is indicated for use with sofosbuvir (with or without ribavirin) for the treatment of HCV genotypes 1 or 3 but SVR rates are reduced in genotype 3 patients with cirrhosis. In January 2016, the fixed dose combination of elbasvir/grazoprevir (Zepatier), an NS5A inhibitor and an NS3/4A protease inhibitor, was approved for use with or without ribavirin for HCV genotypes 1 or 4. The first pangenotypic combination therapy effective in the treatment of all 6 genotypes, sofosbuvir/velpatasvir (Epclusa), was approved in June 2016.

The joint guidelines from the American Association for Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) Recommendations for Testing, Managing, and Treating Hepatitis C continue to be updated with the advent of new therapies and other developments in care.[36] One important section of the updated AASLD/IDSA recommendations includes guidance on "When and in Whom to Initiate Therapy" addressing the limitations of feasibility associated with treating all patients.[37] The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure, as evidenced by an SVR. Patients cured of their HCV infection experience numerous health benefits, including a decrease in liver inflammation and a reduction in the rate of progression of liver fibrosis and mortality from severe extrahepatic manifestations, such as cryoglobulinemic vasculitis, a condition affecting 10% to 15% of HCV-infected patients. While the guidelines initially supported prioritizing treatment to patients who would experience the most benefit from receiving treatment and patients whose treatment would have the greatest impact on reducing further HCV transmission, more recent revisions support treatment for all patients with chronic HCV. The guidelines note a few exceptions to this treat-all approach: patients with a short life expectancy unlikely to be remediated by HCV treatment, transplantation, or other directed therapy.

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With regard to treatment, the guidelines define recommended regimens (favored for most patients), alternative regimens (optimal in a particular subset of patients), as well as regimens that are not recommended (clearly inferior or harmful treatment options). Some of the recommended and alternative regimens outlined in the guidelines, as well as therapy recommendations for special populations, are based on unpublished data and may go beyond the scope of the current FDA-approved labeling for these products. The guidelines also provide treatment recommendations for patients who have failed previous therapy (partial or null responders), patients co-infected with HIV, patients with renal impairment, patients with hepatic impairment, and patients who develop recurrent HCV post liver transplant. These populations and the applicable guideline recommendations are discussed in the "Special Populations" section of this review.

Summary of the AASLD/IDSA HCV Guidelines Recommendations[38,39]

Genotype 1

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 1a – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis:		
	▪ elbasvir/grazoprevir (no baseline high-fold NS5A RAVs)	12	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ paritaprevir/ritonavir/ombitasvir + dasabuvir + weight-based RBV	12	Class I, Level A
	▪ simeprevir + sofosbuvir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ daclatasvir + sofosbuvir	12	Class I, Level B
	Patients **with compensated** cirrhosis:		
	▪ elbasvir/grazoprevir (no baseline high-fold NS5A RAVs)	12	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
Treatment-Experienced (previous failure of PEG-IFN /RBV)	Patients **without** cirrhosis:		
	▪ elbasvir/grazoprevir (no baseline high-fold NS5A RAVs)	12	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ paritaprevir/ritonavir/ombitasvir + dasabuvir + weight-based RBV	12	Class I, Level A
	▪ simeprevir + sofosbuvir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ daclatasvir + sofosbuvir	12	Class I, Level B
	Patients **with compensated** cirrhosis:		
	▪ elbasvir/grazoprevir (no baseline high-fold NS5A RAVs)	12	Class I, Level A
	▪ ledipasvir/sofosbuvir+ weight-based RBV	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A

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Genotype 1 (continued)

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 1a – Alternative Treatments			
Treatment-Naïve	Patients **without** cirrhosis: ▪ elbasvir/grazoprevir + weight-based RBV (high baseline high-fold NS5A RAVs)	16	Class IIa, Level B
	Patients **with compensated** cirrhosis: ▪ paritaprevir/ritonavir/ombitasvir + dasabuvir + weight-based RBV	24	Class I, Level A
	▪ simeprevir + sofosbuvir ± weight-based RBV (no Q80K polymorphism)	24	Class II, Level B
	▪ daclatasvir + sofosbuvir ± weight-based RBV	24	Class IIa, Level B
	▪ elbasvir/grazoprevir + weight-based RBV (high baseline high-fold NS5A RAVs)	16	Class IIa, Level B
Treatment-Experienced (previous failure of PEG-IFN /RBV)	Patients **without** cirrhosis: ▪ elbasvir/grazoprevir + weight-based RBV (high baseline high-fold NS5A RAVs)	16	Class IIa, Level B
	Patients **with compensated** cirrhosis: ▪ paritaprevir/ritonavir/ombitasvir + dasabuvir + weight-based RBV	24	Class I, Level A
	▪ ledipasvir/sofosbuvir	24	Class I, Level A
	▪ elbasvir/grazoprevir + weight-based RBV (high baseline high-fold NS5A RAVs)	16	Class I, Level B
	▪ daclatasvir + sofosbuvir ± weight-based RBV	24	Class IIa, Level B
	▪ simeprevir + sofosbuvir ± weight-based RBV (Q80K variant negative)	24	Class IIa, Level B
Genotype 1b – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis: ▪ elbasvir/grazoprevir	12	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ paritaprevir/ritonavir/ombitasvir + dasabuvir	12	Class I, Level A
	▪ simeprevir + sofosbuvir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ daclatasvir + sofosbuvir	12	Class I, Level B
	Patients **with compensated** cirrhosis: ▪ elbasvir/grazoprevir	12	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ paritaprevir/ritonavir/ombitasvir + dasabuvir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
Treatment-Experienced (previous failure of PEG-IFN /RBV)	Patients **without** cirrhosis: ▪ elbasvir/grazoprevir	12	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ paritaprevir/ritonavir/ombitasvir + dasabuvir	12	Class I, Level A
	▪ simeprevir + sofosbuvir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ daclatasvir + sofosbuvir	12	Class IIa, Level B
	Patients **with compensated** cirrhosis: ▪ elbasvir/grazoprevir	12	Class I, Level A
	▪ ledipasvir/sofosbuvir + weight-based RBV	12	Class I, Level A
	▪ paritaprevir/ritonavir/ombitasvir + dasabuvir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A

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Genotype 1 (continued)

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 1b – Alternative Treatments			
Treatment-Naïve	Patients **with compensated** cirrhosis: ▪ daclatasvir + sofosbuvir ± weight-based RBV ▪ simeprevir + sofosbuvir ± weight-based RBV	 24 24	 Class IIa, Level B Class IIa, Level B
Treatment-Experienced (previous failure of PEG-IFN /RBV)	Patients **with compensated** cirrhosis: ▪ ledipasvir/sofosbuvir ▪ daclatasvir + sofosbuvir ± weight-based RBV ▪ simeprevir + sofosbuvir ± weight-based RBV	 24 24 24	 Class I, Level A Class IIa, Level B Class IIa, Level B
Genotype 1 (regardless of subtype) – Recommended Treatments			
Treatment-Experienced (previous failure of PEG-IFN / RBV + a HCV protease inhibitor [NS3], including telaprevir, boceprevir, or simeprevir)	Patients **without** cirrhosis: ▪ ledipasvir/sofosbuvir ▪ sofosbuvir/velpatasvir ▪ daclatasvir + sofosbuvir ▪ elbasvir/grazoprevir + weight-based RBV (genotype 1b or 1a with no baseline high-fold NS5A RAVs) ▪ elbasvir/grazoprevir + weight-based RBV (genotype 1a with high baseline high-fold NS5A RAVs)	 12 12 12 12 16	 Class I, Level A Class I, Level A Class IIa, Level B Class IIa, Level B Class IIa, Level B
	Patients **with compensated** cirrhosis: ▪ ledipasvir/sofosbuvir ▪ ledipasvir/sofosbuvir + weight-based RBV ▪ sofosbuvir/velpatasvir ▪ daclatasvir + sofosbuvir ± weight-based RBV ▪ elbasvir/grazoprevir + weight-based RBV (genotype 1b or 1a with no baseline high-fold NS5A RAVs) ▪ elbasvir/grazoprevir + weight-based RBV (genotype 1a with high baseline high-fold NS5A RAVs)	 24 12 12 24 12 16	 Class I, Level A Class I, Level A Class I, Level A Class IIa, Level B Class IIa, Level B Class IIa, Level B
Treatment-Experienced (previous failure of simeprevir + sofosbuvir)	Patients **without** cirrhosis: ▪ Defer treatment, pending availability of data, in those who do not have reasons for urgent treatment Patients **with compensated** cirrhosis or other patients who require urgent treatment: ▪ Testing for resistance-associated variants that confer decreased susceptibility recommended in patients with compensated cirrhosis or without urgent treatment needed; treatment should be tailored as follows: – Dual direct acting antiviral therapy is recommended + weight-based RBV (unless contraindicated) – If available, nucleotide-based (e.g., sofosbuvir) triple or quadruple direct acting antiviral therapy may be considered with duration + weight-based RBV (unless contraindicated)	 -- 24 12 to 24	Class IIb, Level C Class II, Level C
Treatment-Experienced (previous failure of sofosbuvir + RBV ± PEG-IFN)	Patients **without** cirrhosis: ▪ ledipasvir/sofosbuvir + weight-based RBV Patients **with compensated** cirrhosis: ▪ ledipasvir/sofosbuvir + weight-based RBV	 12 24	 Class IIa, Level B Class IIa, Level B

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Genotype 1 (continued)

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 1 (regardless of subtype) – Recommended Treatments (continued)			
Treatment-Experienced (previous failure of any nonstructural protein 5A [NS5A] inhibitor)	Patients **without** cirrhosis: ▪ Defer treatment, pending availability of data, in those who do not have reasons for urgent treatment Patients **with compensated** cirrhosis or other patients who require urgent treatment: ▪ Testing for resistance-associated variants that confer decreased susceptibility recommended in patients with compensated cirrhosis or without urgent treatment needed; treatment should be tailored as follows: – Dual direct acting antiviral therapy is recommended + weight-based RBV (unless contraindicated) – If available, nucleotide-based (e.g., sofosbuvir) triple or quadruple direct acting antiviral therapy may be considered with duration + weight-based RBV (unless contraindicated)	-- 24 12 to 24	Class IIb, Level C Class IIb, Level C

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Genotype 2

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 2 – Recommended Treatments			
Treatment-Naïve	Patients **without cirrhosis or with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir	12	Class I, Level A
Treatment-Experienced (previous failure of PEG-IFN/ RBV)	Patients **without cirrhosis or with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir	12	Class I, Level A
Treatment-Experienced (previous failure of sofosbuvir + RBV)	Patients **without cirrhosis or with compensated** cirrhosis: ▪ daclatasvir + sofosbuvir ± weight-based RBV (patients ineligible for interferon) ▪ sofosbuvir/velpatasvir + weight-based RBV	24 12	Class IIa, Level C Class IIa, Level C
Genotype 2 – Alternative Treatments			
Treatment-Naïve	Patients **without** cirrhosis: ▪ daclatasvir + sofosbuvir Patients **with compensated** cirrhosis: ▪ daclatasvir + sofosbuvir	12 16 to 24	Class IIa, Level B Class IIa, Level B
Treatment-Experienced (previous failure of PEG-IFN/ RBV)	Patients **without compensated** cirrhosis: ▪ daclatasvir + sofosbuvir Patients **with compensated** cirrhosis: ▪ daclatasvir + sofosbuvir	12 16 to 24	Class IIa, Level B Class IIa, Level B

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Genotype 3

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 3 – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis: ▪ daclatasvir + sofosbuvir ▪ sofosbuvir/velpatasvir Patients **with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir ▪ daclatasvir + sofosbuvir ± weight-based RBV	 12 12 12 24	 Class I, Level A Class I, Level A Class I, Level A Class IIa, Level B
Treatment-Experienced (previous failure of PEG-IFN/ RBV)	Patients **without** cirrhosis: ▪ daclatasvir + sofosbuvir ▪ sofosbuvir/velpatasvir Patients **with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir + weight based RBV ▪ daclatasvir + sofosbuvir + weight-based RBV	 12 12 12 24	 Class I, Level A Class I, Level A Class I, Level B Class IIa, Level B
Treatment-Experienced (previous failure of sofosbuvir + RBV)	Patients **with compensated or without** cirrhosis: ▪ daclatasvir + sofosbuvir + weight-based RBV ▪ sofosbuvir/velpatasvir + weight based RBV	 24 12	 Class IIa, Level C Class IIa, Level C

There are no alternative regimens listed for Treatment Naïve or Treatment Experienced genotype 3 patients

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Genotype 4

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 4 – Recommended Treatments			
Treatment-Naïve	Patients **with compensated or without** cirrhosis:		
	▪ paritaprevir/ritonavir/ombitasvir + weight-based RBV	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ elbasvir/grazoprevir	12	Class IIa, Level B
	▪ ledipasvir/sofosbuvir	12	Class IIa, Level B
Treatment-Experienced (previous failure of PEG-IFN/ RBV)	Patients **without** cirrhosis:		
	▪ paritaprevir/ritonavir/ombitasvir + weight-based RBV	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ elbasvir/grazoprevir	12	Class IIa, Level B
	▪ elbasvir/grazoprevir + weight-based RBV (those with on-treatment failure)	16	Class IIa, Level B
	▪ ledipasvir/sofosbuvir	12	Class IIa, Level B
	Patients **with compensated** cirrhosis:		
	▪ paritaprevir/ritonavir/ombitasvir + weight-based RBV	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ elbasvir/grazoprevir	12	Class IIa, Level B
	▪ elbasvir/grazoprevir + weight-based RBV (those with on-treatment failure)	16	Class IIa, Level B
	▪ ledipasvir/sofosbuvir + weight-based RBV	12	Class IIa, Level B
Genotype 4 – Alternative Treatments			
Treatment-Experienced (previous failure of PEG-IFN/ RBV)	Patients **with compensated** cirrhosis		
	▪ ledipasvir/sofosbuvir	24	Class IIa, Level B

There is no alternative regimen listed for Treatment-Naïve genotype 4 patients

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Genotypes 5 and 6

Few data are available to help guide decision making in patients with genotypes 5 or 6; however, these genotypes are uncommon in the U.S.

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 5/6 – Recommended Treatments			
Treatment-Naïve	Patients **with or without** cirrhosis: ▪ sofosbuvir/velpatasvir ▪ ledipasvir/sofosbuvir	 12 12	 Class I, Level A Class IIa, Level B
Treatment-Experienced (previous failure of PEG-IFN/ RBV)	Patients **with or without** cirrhosis: ▪ sofosbuvir/velpatasvir ▪ ledipasvir/sofosbuvir	 12 12	 Class IIa, Level B Class IIa, Level C

PEG-IFN = peginterferon; RAV = resistance-associated variants; RBV = ribavirin

Treatments Not Recommended for Any Genotype[40]

Specific regimens may be used in select special populations based on fewer options (e.g., post-transplant genotype 2 patients).

Treatment	Rating
▪ Daily sofosbuvir + weight-based RBV for 24 weeks ▪ PEG-IFN/RBV ± sofosbuvir, simeprevir, telaprevir, or boceprevir ▪ Monotherapy with PEG-IFN, RBV, or direct-acting antiviral	Class IIb, Level A Class IIb, Level A Class III, Level A

Grading System Used to Rate the Level of the Evidence and Strength of the Recommendation for Each Recommendation

Classification

- **Class I –** Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective
- **Class II –** Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment
- **Class IIa –** Weight of evidence and/or opinion is in favor of usefulness and efficacy
- **Class IIb –** Usefulness and efficacy are less well established by evidence and/or opinion
- **Class III –** Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful

Level of Evidence

- **Level A –** Data derived from multiple randomized clinical trials, meta-analyses, or equivalent
- **Level B –** Data derived from a single randomized trial, nonrandomized studies, or equivalent
- **Level C –** Consensus opinion of experts, case studies, or standard of care

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PHARMACOLOGY[41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57]

Interferons

Most interferon compounds are naturally occurring small proteins and glycoproteins produced and secreted by cells in response to viral infections and other synthetic or biological inducers. Peginterferons are produced by binding the large inert polyethylene glycol moiety to interferon molecules, thus decreasing renal clearance, altering metabolism, and increasing the half-life of the interferon molecule.[58] Because of their long half-lives, peginterferons can be administered subcutaneously (SC) once weekly.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events, including the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities, such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells.

Ribavirin

Ribavirin is a nucleoside analog with antiviral activity. Ribavirin is phosphorylated intracellularly to the triphosphate metabolite. Once phosphorylated, ribavirin disrupts cellular purine metabolism by inhibiting inosine monophosphate dehydrogenase, which leads to a decrease in guanosine triphosphate. Ribavirin may also act as a potent RNA virus mutagen and increase the mutation rate of RNA viruses. Typically, RNA viruses have a high mutation rate that enables the virus to evolve rapidly and escape host immune mechanisms; however, the high mutation rate is also associated with the production of nonviable virions. Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C, and ribavirin should not be used alone for this indication.[59] The mechanism of inhibition of HCV RNA by combination therapy with interferon alfa and ribavirin has not been established.

Protease Inhibitors

DAAs are newer medications approved for the treatment of HCV. One group of DAAs are classified as protease inhibitors and consist of simeprevir (Olysio), grazoprevir (available as part of Zepatier), and paritaprevir (available as part of Viekira Pak, Viekira XR, and Technivie). Paritaprevir, grazoprevir, and simeprevir inhibit hepatitis C NS3/4A protease, which is essential for replication of the virus.

NS5B Inhibitors

Sofosbuvir (Sovaldi) and dasabuvir (available as part of Viekira Pak and Viekira XR) represent another group of DAAs classified as a NS5B polymerase inhibitors. These agents inhibit the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. Dasabuvir targets the palm domain of the NS5B polymerase, and is referred to as a non-nucleoside NS5B-palm polymerase inhibitor.

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NS5A Inhibitors

Another group of DAAs are the NS5A inhibitors and consist of elbasvir (available as part of Zepatier), ledipasvir (co-formulated with sofosbuvir and available as Harvoni), ombitasvir (available as part of Viekira Pak, Viekira XR, and Technivie), daclatasvir (Daklinza), and velpatasvir (co-formulated with sofosbuvir and available as Epclusa). These agents inhibit the HCV NS5A, which is essential for viral RNA replication and virion assembly.

Ritonavir

Ritonavir (available as part of Viekira Pak, Viekira XR, and Technivie) is not active against the hepatitis C virus; it is a CYP3A4 inhibitor used to increase plasma concentrations of paritaprevir.

PHARMACOKINETICS[60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76]

Interferons

The half-life of interferon alfa is approximately 5 to 8 hours. Dosing these agents 3 times weekly results in undetectable blood levels of interferon during the remaining 4 days of the week. Pegylation of the interferons has extended the mean steady-state half-life to 40 hours for peginterferon alfa-2b (PEGIntron) and 160 hours for peginterferon alfa-2a (Pegasys), allowing these agents to be given once weekly. The shorter half-life of peginterferon alfa-2b (PEGIntron) results in undetectable levels at day 7 while peginterferon alfa-2a (Pegasys) accumulates over time with multiple dosing.

In patients with end-stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in clearance of peginterferon alfa-2a (Pegasys). There is a 44% reduction in peginterferon alfa-2b (PEGIntron) clearance in patients with creatinine clearance (CrCl) less than 30 mL/min. Dose reductions for both peginterferons are necessary for patients with moderate renal impairment.

Ribavirin

The terminal half-life of ribavirin (Copegus) with multiple dosing is 120 to 170 hours. The half-life of ribavirin (Rebetol) has been reported as 298 hours. Ribavirin (Rebetol) is metabolized by phosphorylation and degradation prior to being renally eliminated.

Simeprevir

Administration of simeprevir (Olysio) with food to healthy subjects increased the relative bioavailability (AUC) by 61% and 69% after a high fat, high caloric (928 kcal), and normal-caloric (533 kcal) breakfast, respectively, and delayed the absorption by 1 hour and 1.5 hours, respectively. Simeprevir is extensively bound to plasma proteins (greater than 99.9%), primarily to albumin and, to a lesser extent, alfa 1-acid glycoprotein. Simeprevir is metabolized in the liver. *In vitro* experiments with human liver microsomes indicated that simeprevir primarily undergoes oxidative metabolism by the hepatic CYP3A system. Involvement of CYP2C8 and CYP2C19 cannot be excluded. Co-administration of simeprevir with moderate or strong inhibitors of CYP3A may significantly increase the plasma exposure of simeprevir, and co-administration with moderate or strong inducers of CYP3A may significantly reduce the plasma exposure of simeprevir. Elimination of simeprevir occurs via biliary excretion. Renal clearance plays an insignificant role in its elimination.

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Sofosbuvir

After oral administration, sofosbuvir (Sovaldi) is rapidly converted to the predominant circulating metabolite GS-331007, which lacks anti-HCV activity *in vitro.* GS-331007 accounts for greater than 90% of drug-related material systemic exposure, while the parent sofosbuvir accounts for approximately 4% of drug-related material. Following oral administration of sofosbuvir under fasting conditions, peak plasma concentrations were observed at 0.5 to 2 hours post-dose and this was not substantially altered when sofosbuvir was administered with a high fat meal. Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The terminal half-life of sofosbuvir is 0.4 hours and is 27 hours for GS-331007. Renal clearance is the predominant elimination pathway.

Ledipasvir

Ledipasvir reaches its mean peak concentration approximately 4 to 4.5 hours after oral administration. The pharmacokinetics of ledipasvir is not significantly altered by meals and can be administered without regard to food. There was no detectable metabolism of ledipasvir by cytochrome P450 isoenzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Ledipasvir is eliminated in the feces primarily unchanged.

Ombitasvir/paritaprevir/ritonavir and dasabuvir

Ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak/Viekira XR) reaches its mean peak concentration approximately 4 to 5 hours after oral administration. The absolute bioavailability of dasabuvir is approximately 70% and the absolute bioavailability of ombitasvir, paritaprevir, and ritonavir was not evaluated. Ombitasvir, paritaprevir, ritonavir, and dasabuvir should always be administered with a meal as the mean AUC is increased under fed conditions. Ombitasvir is predominantly metabolized by amide hydrolysis followed by oxidative metabolism. Paritaprevir is predominantly metabolized by CYP3A4 and, to a lesser extent, by CYP3A5. Ritonavir is predominantly metabolized by CYP3A and, to a lesser extent, by CYP2D6. Dasabuvir is predominantly metabolized by CYP2C8 and, to a lesser extent, by CYP3A. Ombitasvir, paritaprevir, ritonavir, and dasabuvir are primarily eliminated in the feces.

Ombitasvir/paritaprevir/ritonavir

Ombitasvir, paritaprevir, and ritonavir (Technivie) also reaches its mean peak concentration approximately 4 to 5 hours after oral administration. When administered with ritonavir, the absolute bioavailability of ombitasvir and paritaprevir are approximately 48.1% and 52.6%, respectively. Similar to Viekira Pak/Viekira XR, ombitasvir, paritaprevir, and ritonavir should always be administered with a meal as the mean AUC is increased under fed conditions. All components are highly protein-bound. The metabolism and elimination of ombitasvir, paritaprevir, and ritonavir are described above.

Daclatasvir

Daclatasvir (Daklinza) reaches its mean peak concentration approximately 2 hours following oral administration. While food may have a mild effect on AUC, daclatasvir may be taken with or without food. The absolute bioavailability of daclatasvir tablets is 67%. Daclatasvir is metabolized primarily by CYP3A4 and is a substrate of CYP3A. Daclatasvir is primarily eliminated in the feces.

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Elbasvir/grazoprevir

Elbasvir and grazoprevir (Zepatier) reaches its mean peak concentration within 3 hours and 2 hours, respectively, following oral administration. Both components are highly protein-bound and undergo oxidative metabolism, primarily by CYP3A enzymes, with excretion occurring predominantly through the feces (greater than 90%).

Velpatasvir

Velpatasvir reaches its mean peak concentration approximately 3 hours after oral administration. The pharmacokinetics of velpatasvir is not significantly altered by meals and can be administered without regard to food. Velpatasvir is metabolized by cytochrome P450 isoenzymes CYP2B6, CYP2C8, and CYP3A4. Velpatasvir is eliminated primarily by biliary excretion unchanged.

CONTRAINDICATIONS/WARNINGS[77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95]

Contraindications and warnings for an agent also apply when that agent is used as part of a combination regimen.

Interferons

Contraindications

Peginterferon alfa and interferon alfa are contraindicated in patients with autoimmune hepatitis or hepatic decompensation or hypersensitivity to any of the product components.

Peginterferon alfa-2a (Pegasys) is contraindicated in hepatic decompensation (Child-Pugh B and C) in cirrhotic chronic hepatitis C patients before treatment. Peginterferon alfa-2a (Pegasys) is contraindicated in hepatic decompensation in cirrhotic chronic hepatitis C patients co-infected with HIV before treatment.

Peginterferon alfa-2b (PEGIntron) is contraindicated in hepatic decompensation (Child-Pugh B and C) in cirrhotic chronic hepatitis C patients before treatment or during treatment.

Benzyl alcohol is associated with an increased incidence of neurologic and other complications in neonates and infants, which are sometimes fatal; therefore, peginterferon alfa-2a (Pegasys) is contraindicated in neonates and infants.

Peginterferon alfa-2b (PEGIntron) is contraindicated in known hypersensitivity reactions, such as urticaria, angioedema, bronchoconstriction, anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis to interferon alpha or any other product component. Peginterferon alfa-2a (Pegasys) is contraindicated with hypersensitivity to peginterferon alfa-2a or any other component.

Peginterferon alfa-2a and ribavirin combination is contraindicated when given concurrently with didanosine due to reports of fatal hepatic failure and peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis.

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Warnings

All of the alpha interferons indicated for HCV, including peginterferons, have the following boxed warning: alpha interferons cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Serious and severe infections due to bacterial, fungal, or viral pathogens have been reported with the alpha interferons, including some fatal infections. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolved after stopping interferon therapy.

Life-threatening or fatal neuropsychiatric events including suicides, suicidal and homicidal ideation, depression, and relapse of drug addiction/overdose may manifest in patients receiving therapy with peginterferon alfa. Adverse neuropsychiatric events reported with alpha interferons include aggressive behavior, psychoses, hallucinations, bipolar disorder, and mania. These reactions may occur in patients with or without previous psychiatric illness. Patients on therapy should receive close monitoring for the occurrence of depressive symptomatology. Patients with persistently severe or worsening neuropsychiatric signs or symptoms should be withdrawn from therapy. These agents should be used with extreme caution in patients with a history of psychiatric illness.

Additionally, peginterferon (Peg-Intron) should be used with extreme caution in patients with a history of psychiatric disorders. Interferon alfa may be associated with exacerbated symptoms of psychiatric disorders with concurrent psychiatric and substance use disorders. Life-threatening or fatal neuropsychiatric events (e.g., suicide, suicidal or homicidal ideation, aggression, depression, addiction relapse, and overdose) have been reported with this agent in patients with and without a previous psychiatric disorder. If interferon treatment is deemed necessary in patients with a prior history or existence of psychiatric disorder or with a history of substance use disorders, treatment requires individualized drug screening strategies and frequent psychiatric symptom monitoring. Early intervention for re-emergence or development of neuropsychiatric symptoms and substance abuse is recommended.

Peginterferon alfa suppresses bone marrow function and may result in severe cytopenias, including neutropenia and lymphopenia and very rare events of aplastic anemia. It is advised that complete blood counts be obtained pre-treatment and monitored routinely during therapy. Interferon alfa should be discontinued in patients who develop severe decreases in neutrophils ($<0.5 \times 10^9$/L) or platelet counts ($<25 \times 10^9$/L). Severe neutropenia and thrombocytopenia occur with a greater incidence in HIV co-infected patients than monoinfected patients and may result in serious infections or bleeding. Serious bacterial, fungal, and viral infections, some fatal, have been observed in interferon-treated patients. Some infections have been associated with severe neutropenia.

Peginterferon alfa should be used with caution in patients with cardiac disease. Chest pain, changes in blood pressure, supraventricular arrhythmias, and myocardial infarctions have occurred. Patients with a history of significant or unstable cardiac disease should not be treated with peginterferon and ribavirin therapy.

Peginterferon alfa also affects the endocrine system, either causing or aggravating hyperthyroidism or hypothyroidism, as well as hyperglycemia or hypoglycemia. New onset diabetes including Type 1 Diabetes Mellitus has been reported. One study showed thyroid dysfunction occurring in 11.8% of 254 patients being treated for chronic hepatitis C with interferon alfa plus ribavirin combination therapy.[96]

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Neither interferon alfa dosage nor the virologic response to treatment was related to the incidence of thyroid dysfunction, of which two-thirds was hypothyroidism and one-third was hyperthyroidism.

Pulmonary disorders, colitis (ulcerative and hemorrhagic/ischemic), and pancreatitis have occurred following use of peginterferon alfa. Decreases in or loss of vision, retinopathy, retinal vessel thrombosis, optic neuritis, serious retinal detachment, and papilledema are induced or aggravated by treatment with interferon alfa. Cerebral vascular events, both thrombotic and hemorrhagic, have been reported with patients receiving interferon alfa therapy; events occurred in patients with few or no other risk factors for stroke, including patients less than 45 years of age. Due to fever and flu-like symptoms from peginterferon, use caution when using peginterferon in patients with debilitating medical conditions, such as those with a history of pulmonary disease such as chronic obstructive pulmonary disease.

Patients with chronic hepatitis C with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons. Initiation of peginterferon alfa therapy has been reported to cause transient liver abnormalities, which can result in increased ascites, hepatic failure, or death in patients with poorly compensated liver disease. Therapy should be discontinued for any patient developing signs and symptoms of liver failure. There are very little data regarding use of peginterferon alfa in immunosuppressed patients or transplant recipients.

Patients with cirrhosis due to chronic hepatitis C and also infected with HIV who receive highly active antiretroviral therapy (HAART) and interferon alfa-2a, with or without ribavirin, appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART. Patients' clinical status and hepatic function should be closely monitored and peginterferon should be immediately discontinued in patients with hepatic decompensation.

Peginterferon alfa should be used with caution in patients with a history of autoimmune disease.

Ribavirin

Contraindications

Ribavirin is contraindicated in patients with hemoglobinopathies (e.g., thalassemia major, sickle cell anemia). Ribavirin is contraindicated in patients with known hypersensitivity to ribavirin or to any component of the product. Co-administration of ribavirin (Rebetol) and didanosine is contraindicated because exposure to the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) is increased. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis, have been reported in patients receiving both didanosine and ribavirin.

Ribavirin is contraindicated in females who are pregnant and in the male partners of females who are pregnant. Ribavirin is Pregnancy Category X. Ribavirin exposure may cause birth defects and/or death of the exposed fetus. Ribavirin therapy should not be started unless a negative pregnancy test has been obtained immediately prior to the initiation of ribavirin therapy. Patients should use a minimum of 2 effective forms of contraception during therapy and for 6 months after treatment has stopped. Monthly pregnancy testing should be performed during and for 6 months after therapy has been discontinued. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen.

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Ribavirin is contraindicated in patients with autoimmune hepatitis, hepatic decompensation (Child-Pugh B or C) in cirrhotic patients with chronic hepatitis C before or during therapy, and hepatic decompensation in cirrhotic chronic hepatitis C patients with co-infected with HIV before or during therapy.

Warnings

The primary toxicity of ribavirin is hemolytic anemia. Hemolytic anemia was observed in approximately 10% of patients treated with interferon alfa plus ribavirin in clinical trials and usually occurred within 1 to 2 weeks of initiation of ribavirin therapy. Cardiac and pulmonary events have occurred in approximately 10% of patients with hemolytic anemia. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. Caution should be exercised in starting treatment in any patient with an increased risk of severe anemia (e.g., history of gastrointestinal bleeding).

Patients with estimated creatinine clearance < 50 mL/minute should not receive ribavirin.

Severe depression and suicidal or homicidal ideation have been reported in patients taking both ribavirin and interferon.

Protease Inhibitor – simeprevir (Olysio)

Contraindications

Simeprevir (Olysio) in combination with peginterferon and ribavirin is contraindicated with decompensated cirrhosis (moderate to severe hepatic impairment).

Warnings

Patients undergoing treatment for HCV who are receiving DAAs may be at greater risk for hepatitis B virus (HBV) reactivation.[97,98] As a result, the FDA issued a drug safety communication regarding this risk, and labels have been updated to reflect this warning. Prior to initiation of DAAs, patients should be tested for previous or current HBV infection. Those testing positive for a prior or active HBV infection should receive additional monitoring during (not more frequently than every 4 weeks per AASLD) and upon completion of HCV treatment to detect HBV reactivation. Likewise, those testing positive for an active HBV infection should be treated for the HBV infection prior to or in conjunction with DAA therapy for HCV infection. The FDA also required an additional boxed warning regarding this risk for all DAAs.

Rash has been observed in patients receiving simeprevir (Olysio) in combination with peginterferon and ribavirin, including severe rash and rash requiring discontinuation. Rashes occurred most frequently in the first 4 weeks of treatment but can occur at any time during treatment. Patients with mild to moderate rashes should be followed for possible progression of rash. If the rash becomes severe, simeprevir should be discontinued. Patients should be monitored until the rash has resolved.

Photosensitivity reactions reported with simeprevir include burning, erythema, exudation, blistering, and edema. These reactions have been observed with simeprevir in combination with peginterferon and ribavirin, including serious reactions, which resulted in hospitalization. Photosensitivity reactions also occurred most frequently in the first 4 weeks of treatment but can occur at any time during treatment. Sun protective measures should be used and discontinuation of simeprevir should be considered if a photosensitivity reaction occurs.

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Simeprevir contains a sulfonamide moiety. In patients with a history of sulfa allergy, no increased incidence of rash or photosensitivity reactions has been observed. However, there are insufficient data to exclude an association between sulfa allergy and the frequency or severity of adverse reactions observed with the use of simeprevir.

Hepatic failure and decompensation, including fatal cases, have been reported in patients treated with simeprevir in combination with peginterferon alfa and ribavirin. Liver function tests should be assessed prior to treatment and as clinically indicated.

Cases of symptomatic bradycardia, some requiring pacemaker intervention, have been reported in patients taking both amiodarone and sofosbuvir (Sovaldi) with simeprevir. Co-administration of simeprevir and sofosbuvir with amiodarone is not recommended. In patients with no alternative treatment options, cardiac monitoring is recommended.

NS5B Polymerase Inhibitor – sofosbuvir (Sovaldi)

Contraindications

When used in combination with peginterferon and/or ribavirin, all contraindications to peginterferon and ribavirin also apply; see above information on interferons and ribavirin for details.

Warnings

All DAAs carry a boxed warning for HBV reactivation, as described above.[99,100]

Drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of sofosbuvir (Sovaldi). Rifampin and St. John's wort should not be used with sofosbuvir.

Co-administration of sofosbuvir with anticonvulsants (carbamazepine, phenytoin, phenobarbital, or oxcarbazepine), antimycobacterial antibiotics (rifabutin, rifapentine, rifampin), and the HIV protease inhibitor combination tipranavir/ritonavir is not recommended, since it can lead to reduced therapeutic effect of sofosbuvir.

Co-administration of amiodarone with sofosbuvir in combination with another direct acting antiviral is not recommended due to the risk of serious symptomatic bradycardia, particularly in patients also receiving beta-blockers or those with underlying cardiac comorbidities and/or advanced liver disease. In patients with no alternative treatment options, cardiac monitoring is recommended.

Sofosbuvir should not be used with other products containing sofosbuvir.

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NS5A Inhibitors – daclatasvir (Daklinza)

Contraindications

Daclatasvir (Daklinza) is contraindicated with the use of strong inducers of CYP3A, including phenytoin, carbamazepine, rifampin, and St. John's wort.

Warnings

All DAAs carry a boxed warning for HBV reactivation, as described above.[101,102]

Co-administration of amiodarone with daclatasvir (Daklinza) in combination with sofosbuvir is not recommended due to the risk of serious symptomatic bradycardia, particularly in patients also receiving beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease. In patients with no alternative treatment options, cardiac monitoring is recommended.

Combination Products – elbasvir/grazoprevir (Zepatier)

Contraindications

Elbasvir/grazoprevir is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C), and in patients who are taking concomitant OATP1B1/3 inhibitors that are known or expected to significantly increase grazoprevir plasma concentrations, strong CYP3A inducers, or efavirenz.

The following medications are contraindicated with elbasvir/grazoprevir due to drug interactions: anticonvulsants (e.g., phenytoin, carbamazepine), antimycobacterials (e.g., rifampin), herbal products (e.g., St. John's wort), HIV medications (e.g., efavirenz, atazanavir, darunavir, lopinavir, saquinavir, tipranavir), and immunosuppressants (e.g., cyclosporine).

Warnings

All DAAs carry a boxed warning for HBV reactivation, as described above.[103,104]

During clinical trials with elbasvir/grazoprevir with or without ribavirin, 1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the upper limit of normal (ULN). Hepatic laboratory testing needs to be performed prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing needs to be performed at treatment week 12. For ALT elevations on elbasvir/grazoprevir, discontinuation of the drug should be considered if the elevation is greater than 10 times the ULN or if the ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

Concomitant use of elbasvir/grazoprevir with certain drugs may result in significant interactions.

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Combination Products – ledipasvir/sofosbuvir (Harvoni)

Contraindications

There are no contraindications to treatment with ledipasvir/sofosbuvir.

Warnings

All DAAs carry a boxed warning for HBV reactivation, as described above.[105,106]

The concomitant use of ledipasvir/sofosbuvir and P-gp inducers (e.g., rifampin, St. John's wort) may significantly decrease the plasma concentrations of both ledipasvir and sofosbuvir and, therefore, may lead to a reduced therapeutic effect. The combination of ledipasvir/sofosbuvir with P-gp inducers is not recommended. Ledipasvir/sofosbuvir should not be used in combination with other products containing sofosbuvir.

Co-administration of amiodarone with ledipasvir/sofosbuvir is not recommended due to the risk of serious symptomatic bradycardia, particularly in patients also receiving beta-blockers or those with underlying cardiac comorbidities and/or advanced liver disease. In patients with no alternative treatment options, cardiac monitoring is recommended.

Combination Products – ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak, Viekira XR)

Contraindications

Ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh B and C).

Ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) is contraindicated for use with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) is contraindicated with drugs that are strong inducers of CYP3A and CYP2C8 due to the possible reduced efficacy of Viekira Pak.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) is contraindicated for use with drugs that are strong inhibitors of CYP2C8 due to the possible increased in dasabuvir plasma concentrations and the risk of QT prolongation.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) is contraindicated in patients with known hypersensitivity (e.g., toxic epidermal necrolysis [TEN] or Stevens-Johnson syndrome) to ritonavir.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) is contraindicated with the following drugs: alfuzosin, ranolazine, dronedarone, carbamazepine, colchicine, phenytoin, phenobarbital, gemfibrozil, rifampin, lurasidone, pimozide, ergotamine, dihydroergotamine, ergonovine, methylergonovine, ethinyl estradiol-containing medications, such as combined oral contraceptives, cisapride, St. John's wort, lovastatin, simvastatin, pimozide, efavirenz, sildenafil (when dosed for the treatment of pulmonary arterial hypertension), triazolam, and orally-administered midazolam.

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Warnings

All DAAs carry a boxed warning for HBV reactivation, as described above.[107,108]

Hepatic decompensation and failure, including cases requiring liver transplantation or resulting in a fatal outcome, have been reported with ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) use. Acute onset of elevated direct serum bilirubin without ALT elevations characterized most cases, and most occurred within 1 to 4 weeks of treatment onset. For patients with cirrhosis, baseline and every 4-week hepatic laboratory testing should be performed as clinically indicated, and Viekira Pak or Viekira XR should be discontinued in patients who develop hepatic decompensation. Monitoring for signs and symptoms of hepatic decompensation is also recommended.

There is an increased risk of ALT elevations in patients taking ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) with or without ribavirin. Elevations of ALT to greater than 5 times the upper limit of normal (ULN) occurred in approximately 1% of all subjects during clinical trials. ALT elevations typically occurred during the first 4 weeks of treatment and declined within 2 to 8 weeks of onset with continued dosing of Viekira Pak or Viekira XR with or without ribavirin. These ALT elevations were significantly more common in female subjects who were using ethinyl estradiol-containing oral contraceptives, contraceptive patches, or contraceptive vaginal rings. Liver function tests should be performed during the first 4 weeks of starting treatment and as clinically indicated thereafter. Consideration should be given to discontinuing ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) if ALT levels remain persistently greater than 10 times the ULN. Ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) should be discontinued if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalized ratio (INR).

Treatment of HCV/HIV-1 co-infected patients with ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 co-infected patients utilizing ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

Combination Products – ombitasvir/paritaprevir/ritonavir (Technivie)

Contraindications

Ombitasvir, paritaprevir, and ritonavir (Technivie) is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh B and C).

Ombitasvir, paritaprevir, and ritonavir (Technivie) is contraindicated for use with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.

Ombitasvir, paritaprevir, and ritonavir (Technivie) is contraindicated with drugs that are moderate or strong inducers of CYP3A due to the possible reduced efficacy of Technivie.

Ombitasvir, paritaprevir, and ritonavir (Technivie) is contraindicated in patients with known hypersensitivity (e.g., toxic epidermal necrolysis [TEN] or Stevens-Johnson syndrome) to ritonavir.

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Ombitasvir, paritaprevir, and ritonavir (Technivie) is contraindicated with the following drugs: alfuzosin, carbamazepine, colchicine, phenytoin, phenobarbital, rifampin, ergotamine, dihydroergotamine, ergonovine, methylergonovine, ethinyl estradiol-containing medications, such as combined oral contraceptives, St. John's wort, lovastatin, simvastatin, pimozide, efavirenz, sildenafil (when dosed for the treatment of pulmonary arterial hypertension), triazolam, and orally-administered midazolam.

Warnings

All DAAs carry a boxed warning for HBV reactivation, as described above.[109,110]

Hepatic decompensation and failure, including cases requiring liver transplantation or resulting in a fatal outcome, have been reported with ombitasvir, paritaprevir, and ritonavir (Technivie) use. Most cases involved patients with advanced cirrhosis prior to starting Technivie. Acute onset of elevated direct serum bilirubin without ALT elevations characterized most cases, and most occurred within 1 to 4 weeks of treatment onset. For patients with cirrhosis, baseline hepatic laboratory testing and every 4 weeks as clinically indicated should be performed, and Technivie should be discontinued in patients who develop hepatic decompensation. Monitoring for signs and symptoms of hepatic decompensation is also recommended.

There is an increased risk of ALT elevations in patients taking ombitasvir, paritaprevir, and ritonavir (Technivie) with or without ribavirin. Elevations of ALT to greater than 5 times the upper limit of normal (ULN) occurred in approximately 1% of all subjects during clinical trials. ALT elevations typically occurred during the first 4 weeks of treatment and declined within 2 to 8 weeks of onset with continued dosing of Technivie with or without ribavirin. These ALT elevations were significantly more common in female subjects who were using ethinyl estradiol-containing oral contraceptives, contraceptive patches, or contraceptive vaginal rings. Prior to starting therapy with ombitasvir, paritaprevir, and ritonavir (Technivie), ethinyl estradiol-containing medications must be discontinued and an alternative contraception should be used during treatment. Liver function tests should be performed during the first 4 weeks of starting treatment and as clinically indicated thereafter. Consideration should be given to discontinuing ombitasvir, paritaprevir, and ritonavir (Technivie) if ALT levels remain persistently greater than 10 times the ULN. Ombitasvir, paritaprevir, and ritonavir (Technivie) should be discontinued if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalized ratio (INR).

Treatment of HCV/HIV-1 co-infected patients with ombitasvir, paritaprevir, and ritonavir (Technivie) can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 co-infected patients utilizing ombitasvir, paritaprevir, and ritonavir (Technivie) should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

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Combination Products – sofosbuvir/velpatasvir (Epclusa)

Contraindications

When used in combination with ribavirin, all contraindications to ribavirin also apply; see above information on interferons and ribavirin for details.

Warnings

All DAAs carry a boxed warning for HBV reactivation, as described above.[111,112]

Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta-blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Co-administration of amiodarone with sofosbuvir/velpatasvir is not recommended. In patients without alternative viable treatment options, cardiac monitoring, including initial monitoring in an inpatient setting, is recommended.

Sofosbuvir/velpatasvir also carries a warning regarding reduced efficacy when used concomitantly with P-glycoprotein (P-gp) inducers and/or moderate to potent inducers of cytochrome P450, specifically CYP2B6, CYP2C8, and CYP3A4. Concurrent use is not recommended.

Risk Evaluation and Mitigation Strategy (REMS)

None of the agents within this class requires REMS.

DRUG INTERACTIONS[113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129]

Interferon

Concomitant use of peginterferon alfa and theophylline may result in a significant increase in theophylline concentrations. Consider monitoring theophylline levels and adjusting theophylline therapy accordingly during peginterferon therapy. Peginterferon alfa has also been reported to inhibit activity of CYP 450 enzymes, although this interaction is thought to be of minimal clinical significance.

Peginterferons have synergistic toxicities when given with myelosuppressive agents, such as antineoplastics and zidovudine.

Ribavirin

Ribavirin may reduce phosphorylation of lamivudine, stavudine, and zidovudine based on *in vitro* studies. No pharmacokinetic or pharmacodynamic interactions were observed in small studies when ribavirin and lamivudine, stavudine, or zidovudine was co-administered as a part of a multiple drug regimen for the treatment of HCV/HIV co-infected patients. Ribavirin and didanosine co-administration may result in increased exposure to didanosine and its metabolites; closely monitor for toxicities and consider discontinuation with worsening toxicities.

Ribavirin co-administered with azathioprine has resulted in pancytopenia with marked decreases in red blood cells, neutrophils, and platelets. Bone marrow suppression has been reported to occur within 3 to 7 weeks after the concomitant administration with peginterferon and ribavirin with azathioprine. In the 8 reported cases, myelosuppression was reversible over 4 to 6 weeks upon withdrawal of all 3 agents and did not recur upon reintroduction of either treatment alone.

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A retrospective cohort study evaluating the effect of HCV medications on warfarin levels found that ribavirin has an impact on warfarin sensitivity. Thus, the authors recommend increased laboratory monitoring in patients who are using concomitant warfarin to ensure appropriate anticoagulation.[130]

Simeprevir

Co-administration of simeprevir (Olysio) with moderate or strong inducers (e.g., carbamazepine, phenobarbital, phenytoin) or inhibitors (e.g., ritonavir, ketoconazole, clarithromycin) of cytochrome P450 is not recommended and may lead to significantly lower or higher exposure of simeprevir, respectively. Simeprevir inhibits OATP1B1/3 and P-glycoprotein (P-gp) transporters. Co-administration of simeprevir with drugs that are substrates for OATP1B1/3 (statins) and P-gp transport (digoxin) may result in increased plasma concentrations of such drugs.

Some of the potentially significant drug interactions with simeprevir (Olysio) include: digoxin, antiarrhythmics, such as amiodarone, calcium channel blockers, immunosuppressants, including cyclosporine, tacrolimus, sirolimus, PDE-5 inhibitors, including sildenafil, and oral administration of either midazolam or triazolam.

Dose adjustments of HMG CO-A reductase inhibitors including rosuvastatin, atorvastatin, simvastatin, pitavastatin, pravastatin, and lovastatin are warranted when given concomitantly with simeprevir. In general, the lowest necessary dose of the HMG CO-A reductase inhibitor should be utilized. Do not exceed a daily dose of 40 mg when simeprevir is co-administered with atorvastatin.

The following drugs are not recommended to be co-administered with simeprevir: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, erythromycin, clarithromycin, telithromycin, itraconazole, ketoconazole, posaconazole, fluconazole, voriconazole, rifampin, rifabutin, rifapentine, systemic dexamethasone, cisapride, milk thistle, and St. John's wort.

In addition, simeprevir should not be co-administered with several HIV treatment agents including cobicistat-containing products, efavirenz, delavirdine, etravirine, nevirapine, atazanavir, fosamprenavir, darunavir/ritonavir, lopinavir, indinavir, nelfinavir, saquinavir, and tipranavir.

Sofosbuvir

Sofosbuvir (Sovaldi) is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP). Drugs that are potent P-gp inducers in the intestine (e.g., rifampin or St. John's wort) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of sofosbuvir and thus should not be used with sofosbuvir.

In addition, administration of sofosbuvir with carbamazepine, phenytoin, phenobarbital, rifabutin, rifapentine, or tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir and coadministration is not recommended.

Co-administration of sofosbuvir (Sovaldi) and other oral direct acting antivirals, including the combination product ledipasvir/sofosbuvir (Harvoni), with amiodarone may result in serious symptomatic bradycardia, particularly in patients also receiving beta-blockers or those with underlying cardiac comorbidities and/or advanced liver disease. In patients with no alternative treatment options, cardiac monitoring is recommended.

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A retrospective cohort study evaluating the effect of HCV medications on warfarin levels found that sofosbuvir (alone and with either ledipasvir or simeprevir) has an impact on warfarin sensitivity. Thus, the authors recommend increased laboratory monitoring in patients who are using concomitant warfarin to ensure appropriate anticoagulation.[131]

Ledipasvir

Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease the concentration of ledipasvir. Antacids, H_2-receptor antagonists (e.g., famotidine), and proton pump inhibitors (e.g., omeprazole) may all decrease ledipasvir concentrations.

Carbamazepine, oxcarbazepine, phenytoin, and phenobarbital are expected to decrease the concentration of ledipasvir and sofosbuvir and co-administration with these agents is not recommended.

Co-administration of ledipasvir/sofosbuvir with digoxin may increase the concentration of digoxin and therapeutic drug monitoring of digoxin is recommended.

Rifampin and other rifamycin derivatives, including rifabutin and rifapentine, may decrease ledipasvir and sofosbuvir concentrations and co-administration with these agents is not recommended.

Tenofovir concentrations are increased and tenofovir-associated adverse reactions may occur in patients receiving ledipasvir/sofosbuvir in combination with antiretroviral regimens that include tenofovir. No clinically significant drug interactions have been observed when ledipasvir/sofosbuvir is administered with the following antiretroviral agents when they are administered individually and not as part of an HIV-combination regimen: abacavir, atazanavir/ritonavir, darunavir/ritonavir, efavirenz, emtricitabine, lamivudine, raltegravir, rilpivirine, and tenofovir disoproxil fumarate. Concentrations of both ledipasvir and simeprevir are increased when they are coadministered and this combination is not recommended.

St. John's wort decreases both ledipasvir and sofosbuvir concentrations and co-administration is not recommended. Co-administration of ledipasvir/sofosbuvir with rosuvastatin may significantly increase the concentration of rosuvastatin leading to an increased risk of myopathy, including rhabdomyolysis. Co-administration with rosuvastatin is not recommended.

Ombitasvir, paritaprevir, ritonavir with and without dasabuvir

Co-administration of ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) or ombitasvir, paritaprevir, and ritonavir (Technivie) with strong inhibitors of CYP3A may increase paritaprevir and ritonavir concentrations. Co-administration of Viekira Pak or Viekira XR with drugs that inhibit CYP2C8 may increase dasabuvir plasma concentrations. Inhibition of P-gp, BCRP, OATP1B1, or OATP1B3 may increase the plasma concentrations of the various components of Viekira Pak, Viekira XR, or Technivie.

Co-administration of Viekira Pak, Viekira XR, or Technivie with drugs that are substrates of CYP3A, UGT1A1, BCRP, OATP1B1, or OATP1B3 may result in increased plasma concentrations of such drugs due to inhibition by the various components of Viekira Pak, Viekira XR, or Technivie.

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Concomitant therapy with ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) could increase concentrations of the following interacting medications: antiarrhythmics (amiodarone, bepridil, disopyramide, flecainide, lidocaine [systemic], mexiletine, propafenone, quinidine), antifungals (ketoconazole), calcium channel blockers (amlodipine, nifedipine, diltiazem, verapamil), colchicine, corticosteroids (fluticasone), diuretics (furosemide), HMG CoA reductase inhibitors (rosuvastatin, pravastatin), immunosuppressants (cyclosporine, tacrolimus), narcotic analgesics (buprenorphine), antipsychotics (quetiapine), sedatives/hypnotics (alprazolam), and angiotensin receptor blockers (valsartan, losartan, candesartan).

Concomitant therapy with ombitasvir, paritaprevir, and ritonavir (Technivie) could increase concentrations of the following interacting medications: digoxin, amlodipine, antiarrhythmics (amiodarone, bepridil, disopyramide, flecainide, lidocaine [systemic], mexiletine, propafenone, quinidine), antifungals (ketoconazole), calcium channel blockers (amlodipine, nifedipine, diltiazem, verapamil), colchicine, corticosteroids (fluticasone), diuretics (furosemide), HMG CoA Reductase Inhibitors (pravastatin), immunosuppressants (cyclosporine, tacrolimus), narcotic analgesics (buprenorphine), antipsychotics (quetiapine), sedatives/hypnotics (alprazolam), and angiotensin receptor blockers (valsartan, losartan, candesartan).

Concomitant therapy with ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) could decrease the concentration of omeprazole. Concomitant therapy with ombitasvir, paritaprevir, and ritonavir (Technivie) could decrease the concentration of darunavir and omeprazole.

Concomitant therapy with ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) and ombitasvir, paritaprevir, and ritonavir (Technivie) has been shown to interact with the following medications and co-administration is not recommended: certain antifungals (voriconazole), certain HIV antivirals (darunavir/ritonavir, lopinavir/ritonavir, rilpivirine), and certain long acting beta-agonists (salmeterol).

A retrospective cohort study evaluating the effect of HCV medications on warfarin levels found that the combination of ombitasvir, paritaprevir, ritonavir, and dasabuvir has an impact on warfarin sensitivity. Thus, the authors recommend increased laboratory monitoring in patients who are using concomitant warfarin to ensure appropriate anticoagulation.[132]

Daclatasvir

Daclatasvir (Daklinza) is a substrate of CYP3A. Strong CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine) may decrease plasma levels of daclatasvir, while strong CYP3A inhibitors (e.g., clarithromycin, itraconazole, cobicistat, ritonavir, indinavir, nelfinavir, saquinavir) may increase plasma levels. Daclatasvir is contraindicated in patients taking strong CYP3A inducers and a dose increase (90 mg once daily) is recommended in patients taking concomitant moderate CYP3A inducers (e.g., modafinil, efavirenz, etravirine, nevirapine dexamethasone). A dose decrease (30 mg) is recommended in patients using concomitant strong CYP3A inhibitors and additional monitoring is recommended in patients using concomitant moderate CYP3A inhibitors (e.g., atazanavir, ciprofloxacin, darunavir/ritonavir, fosamprenavir).

Daclatasvir is a P-gp, BCRP, OATP1B1, and OAT1NB3 inhibitor. Daclatasvir may increase the effect of buprenorphine, dabigatran, statins, and digoxin. Monitoring for adverse effects as a result of increased exposure is recommended.

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Elbasvir/grazoprevir

Grazoprevir is a substrate of OATP1B1/3 transporters. Co-administration of elbasvir/grazoprevir with drugs that inhibit OATP1B1/3 transporters may result in a significant increase in the plasma concentrations of grazoprevir. As such, co-administration of elbasvir/grazoprevir with OATP1B1/3 inhibitors is contraindicated as discussed above. Elbasvir and grazoprevir are substrates of CYP3A and P-gp, but the role of intestinal P-gp in the absorption of elbasvir and grazoprevir appears to be minimal. Co-administration of moderate or strong inducers of CYP3A with elbasvir/grazoprevir may decrease elbasvir and grazoprevir plasma concentrations, leading to reduced therapeutic effect of elbasvir/grazoprevir. Co-administration of elbasvir/grazoprevir with strong CYP3A inducers or efavirenz is contraindicated. Co-administration of elbasvir/grazoprevir with moderate CYP3A inducers is not recommended. Co-administration of elbasvir/grazoprevir with strong CYP3A inhibitors may increase elbasvir and grazoprevir concentrations. Co-administration of elbasvir/grazoprevir with certain strong CYP3A inhibitors is not recommended.

Concomitant administration with the following agents may decrease the efficacy of elbasvir/grazoprevir: nafcillin, bosentan, modafinil, and etravirine. Concomitant administration with the following agents may increase exposure to elbasvir/grazoprevir: ketoconazole and elvitegravir/cobicistat/emtricitabine/tenofovir (disoproxil fumarate or alafenamide). Use of elbasvir/grazoprevir may increase the exposure of the following agents when used concomitantly: tacrolimus and HMG-CoA reductase inhibitors (e.g., atorvastatin, rosuvastatin, fluvastatin, lovastatin, simvastatin).

Sofosbuvir/velpatasvir

Sofosbuvir and velpatasvir are substrates of P-gp and breast cancer resistance protein (BCRP). Concomitant sofosbuvir/velpatasvir therapy with the following inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 may decrease the concentration of sofosbuvir/velpatasvir: efavirenz, phenytoin, phenobarbital, carbamazepine, oxcarbazepine, rifampin, rifabutin, rifapentine, St. John's wort, and tipranavir/ritonavir. Co-administration is not recommended.

Concomitant therapy with the following medications could decrease the concentration of sofosbuvir/velpatasvir due to decreased gastric pH: antacids (aluminum and magnesium hydroxide), H2-receptor antagonists, and proton-pump inhibitors (PPIs). Separate administration time of antacids by 4 hours. H2-receptor antagonists may be given simultaneously with sofosbuvir/velpatasvir or 12 hours apart at doses ≤ 40 mg twice daily of famotidine or the equivalent. If co-administration with a PPI is unavoidable (e.g., medically necessary), administer sofosbuvir/velpatasvir with food 4 hours prior to administration of omeprazole 20 mg; use with other PPIs has not been studied.

Concomitant therapy with amiodarone is not recommended due to the risk of serious symptomatic bradycardia as described above.

Velpatasvir is an inhibitor of drug transporters P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1. Concomitant therapy with sofosbuvir/velpatasvir could increase concentrations of the following interacting medications: digoxin, topotecan, tenofovir, HMG CoA reductase inhibitors (e.g., atorvastatin, rosuvastatin). Additional monitoring and/or dose adjustments of the concomitant agent may be required; co-administration with topotecan is not recommended.

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ADVERSE EFFECTS[133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149]

Drug	Depression	Fever	Injection Site Reaction	Anemia	Neutropenia	Withdrawal Rate
Monotherapy						
peginterferon alfa-2a (Pegasys) n=559	18	37	22	2	21	11
peginterferon alfa-2b (PEGIntron) n=297	29	22	47	0	6	10–14
Dual Combination Therapy						
peginterferon alfa-2a (Pegasys) + ribavirin n=451	20	41	23	11	27	11
peginterferon alfa-2a (Pegasys) + ribavirin n=55	nr	nr	44	nr	nr	13
peginterferon alfa-2b (PEGIntron) + ribavirin n=511 adults	31	46	75	12	26	10–14
peginterferon alfa-2b (PEGIntron) + ribavirin n=107 pediatric patients	1	80	29	11	33	2
ribavirin + sofosbuvir (Sovaldi) for 24 weeks n=250	nr	4	N/A	6	< 1	< 1

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Adverse Effects (continued)

Drug	Rash	Dysgeusia	Fatigue	Anemia	Neutropenia	Withdrawal Rate
Triple Combination Therapy						
simeprevir (Olysio) plus peginterferon alfa/ribavirin n=781	28	nr	nr	nr	nr	2
peginterferon alfa/ribavirin n=397	20	nr	nr	nr	nr	1
sofosbuvir (Sovaldi) plus peginterferon alfa/ribavirin for 12 weeks n=327	18	nr	59	21	17	2
peginterferon alfa/ribavirin for 24 weeks n=243	18	nr	55	12	12	11

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Adverse Effects (continued)

Drug	Fatigue	Headache	Nausea	Diarrhea	Insomnia	Pruritus	Asthenia	Withdrawal Rate
All Oral Combination Therapy								
daclatasvir (Daklinza)/sofosbuvir for 12 weeks n=152	14	14	8	5	nr	nr	nr	nr
elbasvir/grazoprevir (Zepatier) for 12 weeks n=316	11	10	nr	nr	nr	nr	nr	nr
placebo for 12 weeks n=105	10	9	nr	nr	nr	nr	nr	nr
elbasvir/grazoprevir (Zepatier) for 12 weeks n=105	5	0	nr	2	nr	0	nr	nr
elbasvir/grazoprevir (Zepatier) + ribavirin for 16 weeks n=106	4	6	nr	0	nr	4	nr	nr
ledipasvir/sofosbuvir (Harvoni) for 8 weeks n=215	16	11	6	4	3	nr	nr	0
ledipasvir/sofosbuvir (Harvoni) for 12 weeks n=539	13	14	7	3	5	nr	nr	< 1
ledipasvir/sofosbuvir (Harvoni) for 24 weeks n=326	18	17	9	7	6	nr	nr	1
ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak, Viekira XR) + ribavirin for 12 weeks n=770	34	nr	22	nr	14	18	14	< 1
placebo for 12 weeks n=255	26	nr	15	nr	8	7	7	nr
ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak, Viekira XR) + ribavirin for 12 weeks in patients without cirrhosis n=401	nr	nr	16	nr	12	13	9	< 1

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Adverse Effects (continued)

Drug	Fatigue	Headache	Nausea	Diarrhea	Insomnia	Pruritus	Asthenia	Withdrawal Rate
All Oral Combination Therapy (continued)								
ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak, Viekira XR) for 12 weeks in patients without cirrhosis n=509	nr	nr	8	nr	5	7	4	< 1
ombitasvir, paritaprevir, ritonavir (Technivie) + ribavirin for 12 weeks n=91	15	nr	14	nr	13	7	29	nr
ombitasvir, paritaprevir, ritonavir (Technivie) for 12 weeks n=44	7	nr	9	nr	5	5	25	nr
simeprevir + sofosbuvir n=167	25	21	21	nr	14	11	nr	2
sofosbuvir + velpatasvir (Epclusa) for 12 weeks n=1,035	15	22	9	nr	5	nr	5	< 1
sofosbuvir + velpatasvir (Epclusa) for 12 weeks in patients with decompensated cirrhosis n=87	32	11	15	10	11	nr	nr	5

nr = not reported
N/A = not applicable
Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive.

Other adverse reactions occurring in at least 3% of subjects treated with combination peginterferon, ribavirin, and simeprevir (Olysio) in clinical trials included pruritus (22% versus 20% in placebo group), nausea (22% versus 18%), myalgia (16% versus 13%), and dyspnea (12% versus 8%). In the simeprevir-treated groups, 27% experienced grade 1 hyperbilirubinemia compared to 15% of patients in the placebo arm. Grade 2 hyperbilirubinemia occurred in 18% of simeprevir treated patients versus 9% of patients in the placebo arm.

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The most common adverse events (≥ 20%) for sofosbuvir (Sovaldi) plus ribavirin combination therapy were fatigue and headache. The most common adverse events (≥ 20%) for sofosbuvir plus peginterferon alfa plus ribavirin combination therapy were fatigue, headache, nausea, insomnia, and anemia.

Nearly all patients receiving peginterferon alfa plus ribavirin will experience at least 1 adverse effect as a result of peginterferon alfa (such as neutropenia, thrombocytopenia, depression, thyroid disorders, irritability) and/or ribavirin (such as hemolytic anemia, fatigue, itching, rash, sinusitis). Adverse events tend to be more severe in the initial stages of treatment and can often be managed with analgesics, NSAIDs, and antidepressants. Growth factors, such as erythropoietin and filgrastim (Neupogen®), are sometimes used to counteract the adverse effects of ribavirin and peginterferon alfa.

Cases of pulmonary fibrosis have been reported with peginterferon alfa-2b (PEGIntron).

Treatment adherence enhances SVR in patients with genotype 1 HCV.[150] Therefore, management of adverse effects to maintain patients on at least 80% of interferon or peginterferon alfa and ribavirin therapy for at least 80% of the duration of therapy will likely increase the chance for SVR.

Laboratory abnormalities occurring in less than 5% of patients taking ledipasvir/sofosbuvir (Harvoni) included bilirubin elevations of greater than 1.5 times the upper limit of normal (ULN) and transient, asymptomatic lipase elevations of greater than 3 times the ULN.

Co-administration of sofosbuvir (Sovaldi) and other oral direct acting antivirals, including the combination product ledipasvir/sofosbuvir (Harvoni), with amiodarone may result in serious symptomatic bradycardia, particularly in patients also receiving beta-blockers or those with underlying cardiac comorbidities and/or advanced liver disease. In patients with no alternative treatment options, cardiac monitoring is recommended.

The most common adverse events occurring in at least 10% of patients treated with ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) and ribavirin who were co-infected with HCV/HIV included fatigue (48%), insomnia (19%), nausea (17%), headache (16%), pruritus (13%), cough (11%), irritability (10%), and ocular icterus (10%). Median declines in CD4+ T-cells of 47 cells/mm^3 and 62 cells/mm^3 were observed at the end of 12 and 24 weeks of treatment, respectively. No subject experienced an AIDS-related opportunistic infection.

Adverse events occurring in more than 20% of the 34 post-liver transplant subjects treated with Viekira Pak, Viekira XR, and ribavirin were fatigue (50%), headache (44%), cough (32%), diarrhea (26%), insomnia (26%), asthenia (24%), nausea (24%), muscle spasms (21%), and rash (21%). Ten of the 34 subjects underwent a ribavirin dose modification due to a decrease in hemoglobin and 1 patient required an interruption of ribavirin.

Post-baseline elevations in bilirubin at least 2 times ULN were observed in 15% of patients across all phase 3 studies receiving Viekira Pak or Viekira XR with ribavirin compared to 2% of patients receiving Viekira Pak or Viekira XR alone. These increases were predominantly indirect bilirubin and were attributed to the inhibition of bilirubin transporters OATP1B1/1B3 by paritaprevir, as well as ribavirin-induced hemolysis. In the study involving patients co-infected with HCV/HIV, 54% of subjects experienced total bilirubin elevations greater than 2 times ULN. Approximately half of the HCV/HIV co-infected patients who developed a bilirubin elevation greater than 2 times ULN were also receiving atazanavir.

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Across all phase 3 studies, the mean change in hemoglobin levels from baseline was -2.4 g/dL in patients treated with Viekira Pak or Viekira XR plus ribavirin compared to -0.5 g/dL in patients treated with Viekira Pak or Viekira XR alone. Seven percent of patients treated with Viekira Pak or Viekira XR plus ribavirin required a ribavirin dose reduction secondary to a decrease in hemoglobin levels, 3 subjects received a blood transfusion, and 5 patients were treated with erythropoietin. Only 1 patient discontinued therapy due to anemia. In the subset of HCV/HIV co-infected patients, 11% of patients had at least 1 post-baseline hemoglobin value of less than 10 g/dL and, in the post-liver transplant cohort, 29% of patients had at least 1 post-baseline hemoglobin value of less than 10 g/dL.

Hypersensitivity reactions have been reported with Viekira Pak and Viekira XR.

Skin reactions, including various rashes and rash descriptors (mostly mild), have been reported in approximately 5% to 7% of patients taking ombitasvir, paritaprevir, and ritonavir (Technivie), with and without ribavirin. Bilirubin elevations 2 times the ULN occurred in 5% of patients receiving Technivie with ribavirin in clinical trials. The mean change in hemoglobin levels from baseline in clinical trials was -2.1 g/dL in patients treated with Technivie plus ribavirin compared to -0.4 g/dL in patients treated with Technivie alone. Hypersensitivity reactions and hepatic decompensation have also been reported with Technivie.

Asymptomatic and transient elevations of lipase (greater than 3 x ULN) occurred in 2% of patients taking daclatasvir (Daklinza) and sofosbuvir (Sovaldi) in a 12-week clinical trial.

Additional adverse reactions reported with elbasvir/grazoprevir (Zepatier) include irritability (1%), depression (1%), and abdominal pain (2%). Elevations in serum ALT (5 times ULN, 1%) and bilirubin (2.5 times ULN, 6%) have been reported with elbasvir/grazoprevir. Decreased hemoglobin during treatment has also been reported (mean for 12 weeks treatment, -0.3 g/dL; mean for 16 weeks treatment, -2.2 g/dL); however, hemoglobin normalized following discontinuation.

In clinical trials, asymptomatic lipase elevations > 3 x ULN (2% to 6%) and creatine kinase ≥ 10 x ULN (1% to 2%) occurred more commonly in patients treated with sofosbuvir/velpatasvir (Epclusa) compared to patients treated with placebo (1% and 0%, respectively).

SPECIAL POPULATIONS[151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167]

Pediatrics

An estimated 23,000 to 46,000 children in the U.S. have HCV.[168] The seroprevalence is 0.2% for children ages 6 to 11 years and 0.4% for those 12 to 19 years of age.[169] New HCV infections in children are primarily the result of perinatal transmission.[170] The 2009 AASLD practice guidelines for the treatment of hepatitis C recommend that children ages 2 to 17 years receive the same methods of diagnosis, testing, and treatment criteria as adults. The 2009 guidelines recommend the following as standard treatment for children ages 2 to 17 years: peginterferon alfa-2b (PEGIntron) 60 mcg/m^2 SC weekly with ribavirin 15 mg/kg daily for 48 weeks. The 2011 AASLD guidelines did not cover the treatment of pediatric patients with the exception of the statement that telaprevir (Incivek) and boceprevir (Victrelis), which are no longer available, are not recommended for use in children and adolescents younger than 18 years of age, because the safety and efficacy have not been established in this population.[171] The updated AASLD/IDSA hepatitis C guidelines do not address HCV in pediatric patients.

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In December 2008, peginterferon alfa-2b (PEGIntron) plus ribavirin was approved by the FDA for the treatment of chronic hepatitis C in previously untreated pediatric patients (ages ≥ 3 years). The SVR rate for peginterferon alfa-2b and ribavirin for 48 weeks for genotype 1, 4, or high viral load and genotype 3 was 55%. In a small published trial, safety and efficacy of peginterferon alfa-2b (PEGIntron) plus ribavirin have been evaluated in 30 children (ages 3 to 16 years) with detectable HCV for a minimum of 3 years.[172] Patients were given peginterferon alfa-2b 1 mcg/kg weekly plus ribavirin 15 mg/kg per day for 24 weeks for genotypes 2 or 3 and 48 weeks for genotypes 1 or 4. SVR was achieved by 50% of patients (100% of genotype 3; 12/27 patients with genotypes 1 or 4). For early virologic response (EVR) at week 12, 52% of patients were HCV RNA negative. Three patients discontinued therapy due to adverse effects. Dose reductions of peginterferon alfa-2b were required in 23% of patients due to neutropenia.

In August 2011, peginterferon alfa-2a (Pegasys) plus ribavirin was approved by the FDA for the treatment of chronic hepatitis C in previously untreated pediatric patients 5 to 17 years of age. In a study that randomized 114 patients to receive either peginterferon alfa-2a, 180 mcg/1.73m^2 times body surface area once weekly plus ribavirin 15 mg/kg (n=55) or peginterferon alfa-2a (same dosage) plus placebo (n=59) for 48 weeks, reported SVR rates were 53% in the peginterferon alfa plus ribavirin group versus 21% in the peginterferon alfa monotherapy group ($p<0.001$).[173] For those patients with genotype 1 HCV, SVR was obtained in 47% and 17% of the combination and monotherapy groups, respectively. Neutropenia or anemia leads to dose modification in about 30% of children. At the 2-year follow-up visit, in the 82% of combination therapy and 86% of monotherapy patients available for analysis of durability of response, virologic response was 100% in both groups.

Another published study evaluated peginterferon alfa-2a (Pegasys) in a trial with 14 children ages 2 to 8 years with chronic hepatitis C.[174] Peginterferon alfa-2a (Pegasys) dosing was based on body surface area (BSA) x 180 mcg and administered as once weekly subcutaneous injection for 48 weeks. Pharmacokinetics were evaluated and compared to adult data and determined that dosing based on BSA produced adequate drug levels. SVR was achieved in 43% of patients with genotype 1. No serious adverse events were noted.

The weight and height gain of pediatric patients treated with peginterferon alfa-2b (PEGIntron) and ribavirin lags behind that predictive by normative population data for the entire length of treatment. After about 6 months post-treatment, subjects had weight gain rebounds similar to that predicted by their average baseline weight. After about 6 months post-treatment, height gain stabilized and subjects treated with peginterferon alfa-2b and ribavirin had an average height percentile of 44 percentile, which was less than the average of the normative population and less than their average baseline height (51 percentile). Severely inhibited growth velocity (< 3 percentile) was observed in 70% of patients while on treatment. Of the subjects experiencing severely inhibited growth, 20% had continued inhibited growth velocity (< third percentile) after 6 months of follow-up. Long-term follow-up data in pediatric subjects is too limited to determine overall risk of reduced adult height.

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Pediatric patients treated with peginterferon alfa-2a and ribavirin (Pegasys) show a delay in weight and height increases after 48 weeks of therapy compared with their baseline. Both weight and height for age z-scores, as well as the percentiles of the normative population for subject weight and height, decrease during treatment. On follow-up at 2 years post-treatment, most patients had returned to their baseline normative growth curve percentiles, but 16% of patients remained 15 percentiles or more below their baseline weight curve and 11% remained 15 percentiles or more below their baseline height curve.

Benzyl alcohol is associated with an increased incidence of neurologic and other complications in neonates and infants, which are sometimes fatal; therefore, peginterferon alfa-2a (Pegasys) is contraindicated in neonates and infants.

Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment with ribavirin and off-therapy follow-up.

Safety and effectiveness of ledipasvir/sofosbuvir (Harvoni), ombitasvir/ paritaprevir/ritonavir + dasabuvir (Viekira Pak, Viekira XR), ombitasvir/ paritaprevir/ritonavir (Technivie), simeprevir (Olysio), daclatasvir (Daklinza), elbasvir/ grazoprevir (Zepatier), sofosbuvir (Sovaldi), and sofosbuvir/velpatasvir (Epclusa) have not been established in pediatric patients.

Pregnancy

Ribavirin is Pregnancy Category X. Ribavirin exposure may cause birth defects and/or death of the exposed fetus. Ribavirin is contraindicated in females who are pregnant and in the male partners of females who are pregnant. AASLD/IDSA guidelines for the treatment of HCV state that females who have used ribavirin and sexual partners of male patients who have received ribavirin should not become pregnant for at least 6 months after discontinuation of ribavirin (Class III, Level B).[175]

Peginterferon alfa-2a (Pegasys) and peginterferon alfa-2b (PEGIntron) are Pregnancy Category C.

Ledipasvir/sofosbuvir (Harvoni) and sofosbuvir (Sovaldi) are Pregnancy Category B, while simeprevir (Olysio) is Pregnancy Category C.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) and ombitasvir, paritaprevir, and ritonavir (Technivie) are Pregnancy Category B. Combination therapy with ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant.

When dual or triple therapy is utilized, the Pregnancy Category of the most restrictive individual drug used in the combination regimen should be considered.

No data using daclatasvir (Daklinza), elbasvir/grazoprevir (Zepatier), or sofosbuvir/velpatasvir (Epclusa) in pregnant women are available to provide information regarding risk.

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Ethnicity

Several trials have demonstrated African Americans and Latinos are less likely than non-Hispanic whites to respond to dual therapy with interferon and ribavirin.[176,177,178] The reasons for these differences are not known.[179]

Patients of East Asian ancestry exhibit higher simeprevir (Olysio) exposures, which have been associated with increased frequency of adverse reactions, including rash and photosensitivity. There are insufficient safety data to recommend an appropriate dose for patients of East Asian ancestry. The potential risks and benefits of simeprevir should be carefully considered prior to use in patients of East Asian ancestry. Higher elbasvir and grazoprevir plasma concentrations were observed in Asians compared to Caucasians. Asians experienced a higher rate of late ALT elevation in clinical trials; however, no dose adjustment of grazoprevir/elbasvir is recommended based on race/ethnicity.

Co-infected HCV/HIV Patients

HIV infection is independently associated with advanced liver fibrosis and cirrhosis in patients with HCV co-infection. Per the AASLD/IDSA guidelines, patients with HIV/HCV co-infection should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiviral medications.[180] These guidelines also state that treatment courses < 12 weeks, such as ledipasvir/sofosbuvir (Harvoni) for 8 weeks, are not recommended for co-infected patients (Class IIb, Level C). Differences in treatment regimens in coinfected patients are available in the Dosages section.

Patients Who Have Not Responded, Who Have Partially Responded, or Who Have Relapsed Following Initial Treatment

There are 3 classifications used for patients who have received previous therapy for chronic HCV but who failed treatment. Those whose HCV RNA level did not decline by at least 2-$\log_{10}$ IU/mL by treatment week 12 are classified as null responders. Those whose HCV RNA level had dropped by at least 2-$\log_{10}$ IU/mL at week 12, but still had detectable HCV RNA at week 24, are classified as partial responders. Relapsers are defined as patients who have had undetectable HCV RNA during therapy and then develop measurable HCV RNA after the completion of therapy.

As noted in the Overview section, the AASLD/IDSA guidelines include recommendations for treating patients who relapsed after prior therapy.[181]

Renal Impairment[182]

HCV infection is a major health problem in patients with end stage renal disease (ESRD). The incidence of acute HCV infection during maintenance dialysis is much higher than that in the general population because of the risk of nosocomial transmission.[183]

According to the prescribing information, the peginterferon alfa-2b (PEGIntron) dose should be reduced by 25% for patients with moderate renal impairment (CrCl 30 to 50 mL/minute). For patients with severe renal dysfunction (CrCl 10 to 29 mL/minute), including those on hemodialysis, peginterferon alfa-2b dose should be reduced by 50%. If renal function decreases during treatment, peginterferon alfa-2b should be discontinued. When peginterferon alfa-2b and ribavirin are given in combination, patients with impaired renal function and patients over age of 50 years should be more carefully monitored for the development of anemia.

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The peginterferon alfa-2a (Pegasys) dosage should be reduced to 135 mcg once weekly in patients with a CrCl < 30 mL/minute, including those with ESRD and those on hemodialysis. Signs and symptoms of toxicity should be closely monitored and, if severe or if laboratory abnormalities develop, the dose may be reduced to 90 mcg until symptoms abate. There are no data available on dosage adjustments for renal failure in pediatric patients.

The recommended dosage for ribavirin (Copegus) in patients with renal impairment is as follows: for CrCl 30 to 50 mL/minute, alternating doses of 200 mg and 400 mg every other day; for CrCl < 30 mL/minute and those on hemodialysis, 200 mg daily. The prescribing information for Rebetol states that ribavirin should not be used in patients with a CrCl < 50 mL/minute.

No dosage adjustment of simeprevir (Olysio) or ombitasvir, paritaprevir, and ritonavir (Technivie) is required for patients with mild, moderate, or severe renal impairment. These agents have not been studied in patients with ESRD or those on hemodialysis.

No dosage adjustments are required for ledipasvir/sofosbuvir (Harvoni) in patients with mild or moderate renal impairment. The safety and efficacy of ledipasvir/sofosbuvir have not been evaluated in patients with severe renal impairment (CrCl < 30 mL/min/1.73m^2) or ESRD requiring dialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD.

No dosage adjustment of sofosbuvir (Sovaldi) is required for patients with mild to moderate renal impairment (CrCl ≥ 30mL/min); however, sofosbuvir is not recommended in patients with severe renal impairment (CrCl < 30 mL/min) or patients who require hemodialysis because no dosing data are currently available for this patient population.

No dosage adjustment is recommended for patients taking daclatasvir (Daklinza), elbasvir/grazoprevir (Zepatier), or ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) with any degree of renal impairment.

No dosage adjustment of sofosbuvir/velpatasvir (Epclusa) is required for patients with mild or moderate renal impairment. The safety and efficacy of sofosbuvir/velpatasvir have not been established in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] less than 30 mL/min/1.73 m^2) or ESRD requiring hemodialysis.

The AASLD/IDSA guidelines do not recommend a dose adjustment with the following medications in patients with an estimated CrCl of 30 to 80 mL/min: daclatasvir, ledipasvir/sofosbuvir, paritaprevir/ritonavir/ombitasvir ± dasabuvir, simeprevir, sofosbuvir, or sofosbuvir/velpatasvir (Epclusa) (Class I, Level A). The following are recommended regimens for patients with CrCl less than 30 mL/min or ESRD who are unable to undergo immediate renal transplant: elbasvir/grazoprevir for 12 weeks (genotypes 1a, 1b, or 4; Class IIb, Level B); paritaprevir/ritonavir/ombitasvir with dasabuvir for 12 weeks (genotype 1b; Class IIb, Level B); and peginterferon with reduced dose ribavirin (genotypes 2, 3, 5, or 6; Class IIb, Level B). Ribavirin should be discontinued if the hemoglobin declines by 2 g/dL despite the use of erythropoietin. An alternative regimen for genotype 1a patients with a baseline hemoglobin > 10 g/dL is paritaprevir/ritonavir/ombitasvir with dasabuvir and reduced dose ribavirin for 12 weeks (Class IIb, Level B). Caution should be used due to the potential for hemolysis.[184]

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Hepatic Impairment[185]

FDA-approved labeling states no dosage adjustment of simeprevir (Olysio) is necessary for patients with mild hepatic impairment (Child-Pugh A). Simeprevir is not recommended in patients with decompensated cirrhosis (moderate or severe hepatic impairment [Child-Pugh B or C]).

No dosage adjustment of ledipasvir/sofosbuvir (Harvoni) is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh A, B or C). Clinical and hepatic laboratory monitoring is recommended in patients with decompensated cirrhosis as clinically indicated.

No dosage adjustment of ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) or ombitasvir, paritaprevir, and ritonavir (Technivie) is required for patients with mild hepatic impairment (Child-Pugh A). Viekira Pak, Viekira XR, and Technivie are contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh B and C).

No dose adjustment of sofosbuvir (Sovaldi) is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh A, B, or C).

No dosage adjustment of grazoprevir/elbasvir is recommended in patients with mild hepatic impairment (Child-Pugh A). Grazoprevir/elbasvir is contraindicated in patients with moderate hepatic impairment (Child-Pugh B) and severe hepatic impairment (Child-Pugh C). The safety and efficacy of grazoprevir/elbasvir have not been established in patients awaiting liver transplant or in liver transplant recipients.

No dosage adjustment of sofosbuvir/velpatasvir is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh A, B, or C). Clinical and hepatic laboratory monitoring (including direct bilirubin), as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with sofosbuvir/velpatasvir and ribavirin.

No dose recommendation can be given for simeprevir (Olysio) in patients with moderate or severe hepatic impairment due to higher simeprevir exposures. Safety and efficacy of sofosbuvir (Sovaldi) have not been established in patients with decompensated cirrhosis.

No dosage adjustment is recommended in patients taking daclatasvir (Daklinza) with mild to severe hepatic impairment (Child-Pugh A, B, or C).

Patients with any genotype and decompensated cirrhosis should not receive regimens containing peginterferon or simeprevir; monotherapy with peginterferon, ribavirin, or a direct-acting antiviral; or fixed-dose combination of paritaprevir/ritonavir/ombitasvir and dasabuvir with ribavirin.

The AASLD/IDSA guidelines have specific recommendations for patients who have compensated cirrhosis (mild hepatic impairment; Child-Pugh A) and those with decompensated cirrhosis (moderate or severe hepatic impairment; Child-Pugh B or C); the AASLD/IDSA recommendations for patients with compensated cirrhosis are described in the Overview section.[186]

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The guidelines state patients with decompensated cirrhosis should be referred to a practitioner with expertise in that condition (ideally in a liver transplant center) (Class I, Level C).[187] The recommended regimen for patients with HCV genotype 1 or 4 who have decompensated cirrhosis (Child-Pugh B or C), including those with hepatocellular carcinoma, is ledipasvir/sofosbuvir and low initial dose ribavirin for 12 weeks (Class I, Level A), sofosbuvir/velpatasvir with weight-based ribavirin in those with Child-Pugh B or low initial dose ribavirin in those with Child-Pugh C for 12 weeks (Class I, Level A), or daclatasvir with sofosbuvir and low initial dose ribavirin for 12 weeks (Class I, Level B). For patients with HCV genotype 1 or 4 who have decompensated cirrhosis who are ribavirin ineligible, sofosbuvir/velpatasvir (Class I, Level A), daclatasvir and sofosbuvir (Class II, Level C), or ledipasvir/sofosbuvir (Class II, Level C) for 24 weeks is recommended. For patients with HCV genotype 1 or 4 who have decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed, ledipasvir/sofosbuvir plus low initial dose ribavirin, or sofosbuvir/velpatasvir with weight-based ribavirin in those with Child-Pugh B or low initial dose ribavirin in those with Child-Pugh C for 24 weeks is recommended (Class II, Level C).

For genotypes 2 or 3 patients with decompensated cirrhosis who may or may not be candidates for liver transplantation (including patients with hepatocellular carcinoma), the recommendation is sofosbuvir/velpatasvir with weight-based ribavirin for 12 weeks (Class I, Level A) or daclatasvir and sofosbuvir with low initial dose ribavirin for 12 weeks (Class II, Level B).[188]

The guidelines further state that patients with decompensated cirrhosis should not receive monotherapy with peginterferon, ribavirin, or a direct acting antiviral (Class III, Level A); peginterferon/ribavirin with or without sofosbuvir, simeprevir, telaprevir, or boceprevir (Class IIb, Level A); sofosbuvir and weight-based ribavirin for 24 weeks (Class IIb, Level A); simeprevir-based regimens(Class III, Level B); paritaprevir-based regimens (Class III, Level B); or elbasvir /grazoprevir-based regimens (Class III, Level C).

Polymorphisms

Prior to initiation of simeprevir (Olysio) in combination with sofosbuvir (Sovaldi), screening for NS3 Q80K polymorphism in HCV genotype 1a may be considered. Prior to initiation of simeprevir with peginterferon and ribavirin, screening for NS3 Q80K polymorphism in HCV genotype 1a is strongly recommended and alternative therapy should be considered for patients with this polymorphism.

Consider screening for the presence of NS5A mutations (M28, Q30, L31, and Y93) in cirrhotic genotype 1a patients prior to initiating treatment with daclatasvir (Daklinza) and sofosbuvir with or without ribavirin. Testing for Y93H is recommended for genotype 3 patients without cirrhosis who have failed peginterferon/ribavirin and will begin treatment with daclatasvir plus sofosbuvir or sofosbuvir/velpatasvir; if Y93H is present, ribavirin should be included as part of the regimen.

Screening patients with genotype 1a infection for the presence of NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with elbasvir/grazoprevir (Zepatier) to determine the dosage regimen and duration. SVR12 rates were lower in genotype 1a-infected patients with 1 or more baseline NS5A resistance-associated polymorphisms at amino acid positions M28, Q30, L31, or Y93.

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Post-Liver Transplantation

The safety and efficacy of peginterferon alfa, alone or in combination with ribavirin, or simeprevir (Olysio) for the treatment of chronic HCV infection in liver or other organ transplant recipients have not been established.

The AASLD/IDSA guidelines provide treatment recommendations for treatment-naïve and treatment-experienced patients who develop recurrent HCV after liver transplantation.[189] In genotype 1 or 4 infection in the allograft patients who are treatment-naïve or treatment-experienced, including those with compensated cirrhosis, the recommended treatment regimens are ledipasvir/sofosbuvir with weight-based ribavirin (Class I, Level A) or daclatasvir with sofosbuvir and low initial dose ribavirin (Class I, Level B) for 12 weeks. In genotype 1 or 4 infection in the allograft patients who are treatment-naïve with compensated liver disease but are ribavirin ineligible, the recommended regimens are ledipasvir/sofosbuvir (Class I, Level B) or daclatasvir/sofosbuvir (Class II, Level C) for 24 weeks. In treatment-naïve or treatment-experienced genotype 1 or 4 infection in the allograft patients with decompensated cirrhosis, the recommended regimen is ledipasvir/sofosbuvir with low initial dose ribavirin for 12 weeks (Class I, Level B). An alternative regimen for patients with HCV genotype 1 in the allograft with compensated cirrhosis is sofosbuvir plus simeprevir, with or without weight-based ribavirin, for 12 weeks (Class I, Level B). An alternative regimen for patients with Metavir fibrosis stage F0 to F2 due to HCV genotype 1 in the allograft is ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak, Viekira XR) plus weight-based ribavirin for 24 weeks (Class I, Level B).

Recommended regimens for treatment-naïve or treatment-experienced patients with genotype 2 HCV infection in the allograft, including those with compensated cirrhosis, are daclatasvir/sofosbuvir with low initial dose ribavirin for 12 weeks (Class II, Level A) or sofosbuvir and weight-based ribavirin for 24 weeks (Class II, Level C).[190] In this same population, the recommended regimen for ribavirin ineligible patients is daclatasvir with sofosbuvir for 24 weeks (Class II, Level C). Treatment-naïve genotype 2 patients with decompensated cirrhosis should be treated with sofosbuvir and ribavirin (titrated to weight-based dosing) for 24 weeks (Class II, Level C).

The recommended regimen for treatment-naïve or treatment-experienced patients with genotype 3 HCV infection in the allograft, including those with compensated cirrhosis, is daclatasvir with sofosbuvir and low initial dose ribavirin for 12 weeks (Class II, Level A). Daclatasvir with sofosbuvir for 24 weeks is recommended when the patient is ineligible for ribavirin (Class II, Level C).[191]

The following regimen is not recommended in patients with HCV infection of the allograft with compensated cirrhosis: elbasvir/grazoprevir-based regimens (Class III, Level C). The following regimens are not recommended in patients with HCV infection of the allograft with decompensated cirrhosis: regimens containing simeprevir (Class III, Level B); paritaprevir/ombitasvir/ritonavir with or without dasabuvir (Class III, Level B); or elbasvir/grazoprevir-based regimens (Class III, Level C).

Other

Clinical studies of simeprevir did not include sufficient numbers of patients older than 65 years to determine whether they respond differently from younger patients. No dose adjustment of simeprevir is required in geriatric patients.

No differences in safety or efficacy have been seen in patients aged 65 and over; therefore, no dose adjustment of sofosbuvir (Sovaldi) is warranted in geriatric patients.

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A higher rate of late ALT elevation was observed in subjects aged 65 years and older in clinical trials with elbasvir/grazoprevir (Zepatier); however, no dosage adjustment of grazoprevir/elbasvir is recommended in geriatric patients.

Higher elbasvir and grazoprevir plasma concentrations were observed in females compared to males. Females experienced a higher rate of late ALT elevation in clinical trials; however, no dose adjustment of grazoprevir/elbasvir is recommended based on gender.

HCV-infected patients, regardless of genotype, with hepatocellular carcinoma meeting the Milan criteria (defined as the presence of a tumor 5 cm or less in diameter in patients with single hepatocellular carcinomas and no more than 3 tumor nodules, each 3 cm or less in diameter in patients with multiple tumors and no extrahepatic manifestations of the cancer or evidence of vascular invasion of the tumor) have been treated with sofosbuvir 400 mg and weight-based ribavirin daily for 24 to 48 weeks or until the time of liver transplantation, whichever occurred first. The primary endpoint of post-transplant virologic response (pTVR) defined as HCV RNA less than the lower limit of quantification (LLOQ) at 12 weeks post-transplant, was met in 64% of evaluable subjects who had reached the 12-week, post-transplant time point. The safety profile of sofosbuvir and ribavirin in HCV-infected patients prior to liver transplantation was comparable to that observed in subjects treated with sofosbuvir and ribavirin in phase 3 clinical trials.

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DOSAGES[192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208]

Combination Therapy

The AASLD/IDSA guidelines recommend combination therapy for the treatment of all HCV patients. For regimens containing simeprevir (Olysio) with peginterferon and ribavirin, the total duration of therapy depends on viral response, as measured at week 4 or any week thereafter. Daclatasvir (Daklinza), elbasvir/grazoprevir (Zepatier), ledipasvir/sofosbuvir (Harvoni), ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak, Viekira XR), ombitasvir/paritaprevir/ritonavir (Technivie), sofosbuvir (Sovaldi), and sofosbuvir/velpatasvir (Epclusa) dosing does not involve response-guided therapy. Other factors influencing the choice of agent, as well as the duration of therapy, include HCV genotype, whether the patient has cirrhosis, whether or not the patient is interferon/ribavirin intolerant, and whether the patient is treatment-naïve or has been previously treated.

Peginterferon alfa-2a + ribavirin should be discontinued in patients who develop hepatic decompensation during treatment.

ribavirin

Drug	Adult Dosage	Availability
ribavirin (Copegus)	As listed below for combination therapy	Tablet: 200 mg
ribavirin (Rebetol)		Capsule: 200 mg (generic only) Oral solution: 40 mg/mL
ribavirin (RibaPak)		Dose Packs (28-day supply): ▪ 800 mg/day (400 mg tablets in quantities of 14 or 56) ▪ 1,000 mg/day (400 mg + 600 mg tablets in quantities of 7 or 28 tablets of each strength) ▪ 1,200 mg/day: (600 mg tablets in quantities of 14 or 56)
ribavirin (Ribasphere)		Capsule: 200 mg Tablets: 200, 400, 600 mg
ribavirin (Moderiba)		Tablets: 200 mg Dose Packs (7-day supply): ▪ 600 mg/day (200 mg + 400 mg tablets in quantities of 7 tablets of each strength) ▪ 800 mg/day (400 mg in quantities of 14) ▪ 1,000 mg/day (400 mg + 600 mg tablets in quantities of 7 tablets of each strength) ▪ 1,200 mg/day (600 mg tablets in quantities of 14)

Dose modifications may be necessary due to adverse effects such as neutropenia, thrombocytopenia, depression, progressive increases in ALT values over baseline, and impaired renal function. Consult prescribing information for dosage adjustments.

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Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Dual Combination Therapy			
peginterferon alfa-2a (Pegasys) + ribavirin	Genotypes 1, 4: 180 mcg SC once weekly plus ribavirin (1,000 mg per day if < 75 kg or 1,200 mg per day if ≥ 75 kg)	48 weeks	SDV: 180 mcg/1 mL Autoinjector (ProClick): 135 mcg/0.5 mL, 180 mcg/0.5 mL Prefilled syringe: 180 mcg/0.5 mL
	Genotypes 2, 3: 180 mcg SC once weekly plus ribavirin 400 mg twice daily	24 weeks	
	Co-infection with HIV (regardless of genotype): 180 mcg SC once weekly plus ribavirin 400 mg twice daily	48 weeks	
	Age 5 to 17 years: 180 mcg/1.73 m^2 SC once weekly plus ribavirin 15 mg/kg/day orally with food in 2 divided doses	Genotype 1: 48 weeks	
		Genotypes 2 and 3: 24 weeks	
peginterferon alfa-2b (PEGIntron) + ribavirin	Age ≥ 18 years: 1.5 mcg/kg SC once weekly plus ribavirin 800 to 1,400 mg per day, based on body weight, in 2 divided doses Age 3–17 years: 60 mcg/m^2/week plus ribavirin 15 mg/kg/day orally with food in 2 divided doses Patients who reach their 18 years while receiving therapy should remain on the pediatric dosing regimen	Genotype 1: 48 weeks	SDV: powder for injection (with diluent and syringes) 50, 80, 120, 150 mcg Redipen: 50, 80, 120, 150 mcg/0.5 mL
		Genotypes 2 and 3: 24 weeks	
		Retreatment of prior treatment failure: 48 weeks, for all genotypes	
Triple Combination Therapy			
sofosbuvir (Sovaldi) + peginterferon/ribavirin	400 mg orally once daily plus weight-based ribavirin (1,000 mg per day if < 75 kg or 1,200 mg per day if ≥ 75 kg)	Genotype 1 or 4: 12 weeks	400 mg tablet

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Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Triple Combination Therapy *(continued)*			
simeprevir (Olysio) plus peginterferon/ribavirin	150 mg daily with food plus weekly peginterferon and weight-based ribavirin (1,000 mg per day if < 75 kg and 1,200 mg per day if ≥ 75 kg) (Screening genotype 1a patients for the presence of NS3 Q80K polymorphism is strongly recommended prior to initiation)	Genotype 1 or 4 (treatment-naïve and prior relapsers) with or without cirrhosis who are not co-infected with HIV or without cirrhosis who are co-infected with HIV: 12 weeks in combination with peginterferon and ribavirin; Peginterferon and ribavirin therapy is continued beyond the 12 weeks for a total of 24 weeks of treatment; Peginterferon and ribavirin therapy should be continued beyond the 12 weeks for a total of 48 weeks of treatment in patients with cirrhosis and HIV co-infection; Genotype 1 or 4 (prior non-responders): 12 weeks in combination with peginterferon and ribavirin; Peginterferon and ribavirin therapy is continued beyond the 12 weeks for a total of 48 weeks of treatment	150 mg capsule

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Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Oral Combination Therapy			
daclatasvir (Daklinza)/sofosbuvir with or without ribavirin*	60 mg orally once daily in combination with sofosbuvir 400 mg orally once daily with or without ribavirin Ribavirin should be added to the regimen for genotype 1 patients with decompensated cirrhosis (Child-Pugh B or C) and post-transplant patients Ribavirin should be added to the regimen for genotype 3 patients with compensated (Child-Pugh A) or decompensated (Child-Pugh B or C) cirrhosis and post-transplant patients Ribavirin dosing: Genotype 1 or 3 with Child-Pugh A: 1,000 mg/day for patients < 75 kg and 1,200 mg/day for patients ≥ 75 kg Genotype 1 or 3 with Child-Pugh B or C or post-transplantation: 600 mg/day and increasing to 1,000 mg/day as tolerated	Genotype 1 or 3: 12 weeks Dosing is the same regardless of HIV coinfection	daclatasvir 30, 60, 90 mg
elbasvir/grazoprevir (Zepatier) with or without ribavirin	Fixed dose combination: elbasvir 50 mg/grazoprevir 100 mg orally one daily with or without food and with or without ribavirin Ribavirin should be added to the regimen for genotype 1a treatment-naïve or PegIFN/RBV-experienced patients with baseline NS5A polymorphisms, genotype 1a or 1b who are PegIFN/RBV/NS3/4A PI-experienced, and genotype 4 patients who are PegIFN/RBV-experienced Ribavirin dosing: weight based (range, 800 to 1,200 mg/day) administered in 2 divided doses with food; dosing adjusted for renal impairment	Genotype 1a (without baseline NS5A polymorphisms)† or 1b– treatment naïve, PegIFN/RBV-experienced, PegIFN/RBV/NS3/4A PI-experienced: 12 weeks Genotype 1a (with baseline NS5A polymorphisms)†– treatment naïve or PegIFN/RBV-experienced: 16 weeks‡ Genotype 4– treatment naïve: 12 weeks Genotype 4– PegIFN/RBV-experienced: 16 weeks	50/100 mg fixed-dose tablet

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Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Oral Combination Therapy *(continued)*			
ledipasvir/sofosbuvir (Harvoni) with or without ribavirin	Fixed dose combination: ledipasvir 90 mg/ sofosbuvir 400 mg orally once daily with or without ribavirin Ribavirin should be added to the regimen for genotype 1 treatment-naïve and treatment-experienced patients with decompensated cirrhosis (Child-Pugh B or C) Ribavirin should be added to the regimen for genotype 1 or 4 patients treatment-naïve and treatment-experienced liver transplant recipients with compensated (Child-Pugh A) cirrhosis or without cirrhosis Ribavirin dosing: ▪ Noncirrhotic or Child-Pugh A cirrhosis post-transplantation: 1,000 mg/day for patients < 75 kg and 1,200 mg for patients ≥ 75 kg ▪ Child-Pugh B or C: 600 mg once daily and increasing to 1,000 mg/day or 1,200 mg/day weight-based dosing as tolerated	Genotype 1 – treatment naïve (with compensated cirrhosis [Child-Pugh A] or without cirrhosis): 12 weeks[‖] Genotype 1 – treatment-experienced (without cirrhosis):[¶] 12 weeks Genotype 1 – treatment-experienced[¶] with compensated cirrhosis:[¶] 24 weeks[**] Genotype 1 – treatment-naïve or experienced (with decompensated cirrhosis): 12 weeks with ribavirin Genotype 1 or 4 – treatment naïve or experienced[¶] liver transplant recipients (with compensated cirrhosis or without cirrhosis): 12 weeks with ribavirin Genotypes 4, 5, or 6– treatment-naïve or treatment-experienced[¶] with compensated cirrhosis or without cirrhosis: 12 weeks Patients co-infected with HIV/HCV should be treated in the same manner described above	90/400 mg fixed-dose tablet

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Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Oral Combination Therapy *(continued)*			
ombitasvir/paritaprevir/ritonavir plus dasabuvir (Viekira Pak) ± ribavirin[††,‡‡]	Combination: 2 ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and 1 dasabuvir 250 mg tablet twice daily (morning and evening) with a meal ± weight-based ribavirin (< 75 kg = 1,000 mg and ≥ 75 kg = 1,200 mg)	Genotype 1a (without cirrhosis): 12 weeks in combination with ribavirin Genotype 1a (with compensated cirrhosis): 24 weeks in combination with ribavirin[‡‡] Genotype 1b (without cirrhosis or with compensated cirrhosis): 12 weeks	ombitasvir/ paritaprevir/ ritonavir 12.5/75/50 mg fixed-dose tablet, dasabuvir 250 mg tablet
ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira XR) ± ribavirin[††,‡‡]	Combination: 3 ombitasvir/paritaprevir/ritonavir/dasabuvir 8.33/50/33.3/200 mg tablets once daily with a meal ± weight-based ribavirin (< 75 kg = 1,000 mg and ≥ 75 kg = 1,200 mg)	Genotype 1a (without cirrhosis): 12 weeks in combination with ribavirin Genotype 1a (with compensated cirrhosis): 24 weeks in combination with ribavirin[‡‡] Genotype 1b (without cirrhosis or with compensated cirrhosis): 12 weeks	ombitasvir/ paritaprevir/ ritonavir/ dasabuvir 8.33/50/33.3/200 mg fixed-dose tablet
ombitasvir, paritaprevir, ritonavir (Technivie) + ribavirin	Combination: 2 ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) with a meal + weight-based ribavirin (< 75 kg = 1,000 mg and ≥ 75 kg = 1,200 mg)	Genotype 4 (without cirrhosis or with compensated cirrhosis): 12 weeks[lll]	ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg fixed-dose tablet
sofosbuvir (Sovaldi) plus ribavirin	sofosbuvir 400 mg orally once daily plus weight-based ribavirin (<75 kg=1,000 mg and ≥75 kg=1,200 mg) Dosage reductions are not recommended	Genotype 2: 12 weeks Genotype 3: 24 weeks Patients with hepatocellular awaiting liver transplantation: up to 48 weeks or until time of liver transplant Genotype 1 patients who are interferon ineligible: 24 weeks HCV/HIV-1 co-infected patients with genotype 2: 12 weeks HCV/HIV-1 co-infected patients with genotype 3: 24 weeks	400 mg tablet
sofosbuvir (Sovaldi) plus simeprevir (Olysio)	sofosbuvir 400mg orally once daily plus simeprevir 150 mg orally once daily (Screening genotype 1a patients for the presence of NS3 Q80K polymorphism may be considered prior to initiation)	Genotype 1 (without cirrhosis): 12 weeks Genotype 1 (with cirrhosis): 24 weeks	400 mg tablet, 150 mg capsule

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Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Oral Combination Therapy *(continued)*			
sofosbuvir/velpatasvir (Epclusa)	Fixed dose combination: sofosbuvir 400 mg/velpatasvir 100 mg orally once daily with or without food and with or without ribavirin Ribavirin should be added to the regimen for patients with decompensated cirrhosis Ribavirin dosing is weight based: 1,000 mg for patients < 75 kg and 1,200 mg/day for patients ≥ 75 kg divided and administered twice daily with food	Genotypes 1, 2, 3, 4, 5, and 6 (without cirrhosis or with compensated cirrhosis): 12 weeks Genotypes 1, 2, 3, 4, 5, and 6 (with decompensated cirrhosis): 12 weeks in combination with ribavirin	400/100 mg fixed dose tablet

* Optimal duration of daclatasvir and sofosbuvir with or without ribavirin have not been established in genotype 3 patients with cirrhosis or genotype 1 patients with Child-Pugh C cirrhosis.

† Testing for the presence of virus with NS5A resistance-associated polymorphisms in genotype 1a patients is recommended prior to initiating grazoprevir/elbasvir. SVR12 rates were lower in genotype 1a-infected patients with 1 or more baseline NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93.

‡ The optimal grazoprevir/elbasvir-based treatment regimen and duration of therapy for PegIFN/RBV/PI-experienced genotype1a-infected patients with 1 or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, and 93 has not been established.

‖ Treatment with 8 weeks of ledipasvir/sofosbuvir can be considered for treatment-naïve patients without cirrhosis who have a baseline HCV RNA less than 6 million IU/mL.

¶ Treatment-experienced patients include those who have failed a PegIFN/RBV based regimen with or without an HCV protease inhibitor.

** A 12-week regimen with ribavirin may be considered in treatment-experienced patients who are eligible for ribavirin.

†† Viekira Pak/Viekira XR: Patients with HCV/HIV-1 co-infection, follow the dosage recommendations per genotype. In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score ≤2), the recommended duration of Viekira Pak/Viekira XR with ribavirin is 24 weeks.

‡‡ Viekira Pak/Viekira XR administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history (however, patients who were prior null responders to peginterferon/RBV had more virologic failures on 12-week regimen).

‖‖ Treatment without ribavirin for 12 weeks may be considered in treatment-naïve patients without cirrhosis who are unable to take or tolerate ribavirin.

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CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and chronic hepatitis C for the FDA-approved indications. Randomized, controlled comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Due to the chronic nature, course of disease progression, and treatment duration for hepatitis C, many clinical trials lack blinding. Open-label trials have been included below upon initial approval in the absence of blinded studies. Studies performed in the U.S. were given preference since genotype 1 is most common in the U.S. and has been associated with lower SVR. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Studies of peginterferon alfa-2b (PegIntron) and peginterferon alfa-2a (Pegasys) with ribavirin had shown efficacy but they have been removed from this review since no longer considered the standard of care.[209,210,211,212] Likewise, the combination of simeprevir (Olysio) with peginterferon and ribavirin demonstrated efficacy in clinical trials but is no longer considered the standard of care.[213,214]

Approval of (ombitasvir/paritaprevir/ritonavir/dasabuvir) Viekira XR was based on efficacy data established with Viekira Pak (ombitasvir/paritaprevir/ritonavir + dasabuvir).[215]

sofosbuvir (Sovaldi) and ribavirin

POSITRON: This randomized, double-blinded, placebo-controlled study evaluated sofosbuvir in patients with genotypes 2 and 3 that were interferon intolerant as demonstrated during a prior course of treatment, interferon ineligible due to medical history, or unwilling to take interferon.[216] Most patients had no prior HCV treatment (81%). A total of 278 patients were administered dual therapy, sofosbuvir plus ribavirin, or placebo for 12 weeks. Study drug was superior to placebo with SVR12 rates of 78% versus 0% for placebo. In the study drug arm, higher SVR12 rates were reported in patients with genotype 2 compared to those with genotype 3 (93% versus 61%, $p<0.0001$). In addition, patients without cirrhosis had higher SVR12 compared to those with cirrhosis (81% verus 61%). The overall relapse rate was 20%, 5% of patients with genotype 2 relapsed, and 38% with genotype 3. No virologic resistance was detected in patients who did not have a sustained virologic response.

FUSION: This randomized, double-blinded, active-controlled study evaluated dual therapy, sofosbuvir plus ribavirin, for 12 or 16 weeks in 201 treatment-experienced patients with genotypes 2 and 3.[217] Approximately 25% of subjects had prior nonresponse to an interferon-based regimen, and 75% had prior relapse or breakthrough. The SVR12 rate was 50% in the 12-week group and 71% in the 16-week group, this difference was statistically significant. In both treatment groups, subjects with genotype 2 had higher SVR12 rates compared to genotype 3. Extending the treatment duration by 4 weeks

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resulted in an increased SVR12 rate for genotype 2 from 82% to 89%, and for genotype 3 from 30% to 62%. Relapse rate for genotype 2 was 18% and 11%, for 12 versus 16 weeks of therapy, respectively; relapse rate for genotype 3 was 66% and 38%, for 12 versus 16 weeks of therapy, respectively. Presence of cirrhosis was associated with a decreased rate of SVR. No virologic resistance was detected in patients who did not have a sustained virologic response.

FISSION: This randomized, open-label, active-controlled trial enrolled 499 treatment-naïve patients to evaluate, dual therapy, sofosbuvir plus weight-based ribavirin, for 12 weeks compared to peginterferon 180 mcg/week plus ribavirin 800 mg per day for 24 weeks for the treatment of HCV genotype 2 and 3.[218] The overall SVR12 rate was 67% in each treatment group; for those with genotype 2, 95% SVR12 was associated with sofosbuvir plus ribavirin, and 78% for peginterferon plus ribavirin; for those with genotype 3, 56% SVR12 was associated with sofosbuvir plus ribavirin and 63% for peginterferon plus ribavirin. Greater relapse rate was seen for genotype 3, compared to genotype 2, regardless of treatment regimen. No drug-resistance was detected in the 74 patients that relapsed. With the exception of dizziness and anemia, all events occurring in at least 10% of patients were more common among patients receiving peginterferon than among those receiving sofosbuvir.

sofosbuvir (Sovaldi) and ribavirin in genotype 1 (treatment-naïve), 2 or 3 (treatment-naïve and experienced) HCV/HIV-1 co-infections

PHOTON-1:[219] This was an open-label, phase 3, clinical trial evaluating the 12 or 24 weeks of dual therapy, treatment with sofosbuvir and ribavirin, in patients with genotype 1 (treatment-naïve), 2 or 3 (treatment-naïve and experienced) HCV co-infected with HIV-1. Patients received 400 mg sofosbuvir and weight-based ribavirin daily for 12 or 24 weeks based on genotype and prior treatment history. Patients were either not on antiretroviral therapy with a CD4+ cell count >500 cells/mm^3 or had virologically suppressed HIV-1 with a CD4+ cell count >200 cells/mm^3. Efficacy data for 210 patients are reported. In the trial, 76% (95% confidence interval [CI], 67 to 84) of genotype 1 HCV treatment-naïve patients receiving 24 weeks of therapy achieved a SVR 12. SVR12 for genotypes 2 and 3 was 88 (95% CI, 70 to 98) and 67% (95% CI, 51 to 80), respectively. All patients in the study who did not achieve SVR12 had viral relapse after cessation of therapy, with the exception of 2 participants who were non-adherent to study drugs.

simeprevir (Olysio) and sofosbuvir (Sovaldi) in patients with HCV genotype 1a and mild cirrhosis

An open-label, single-center, randomized study evaluated the efficacy of simeprevir (150 mg/day) with sofosbuvir (400 mg/day) versus peginterferon alfa-2b (1.5 mcg/kg/week) plus ribavirin (1,000 to 1,200 mg/day) and sofosbuvir (400 mg/day) for 12 weeks in adult HCV genotype 1a patients with mild cirrhosis (Child-Pugh A) (n=82).[220] The majority of patients were treatment-experienced (61%), while 39% were treatment-naïve. Forty-eight percent were African-American. The primary endpoint was SVR12, and a greater number of patients taking the simeprevir/sofosbuvir regimen achieved SVR12 compared to those in the interferon containing regimen (93% versus 75%, respectively; p=0.02). Overall, the simeprevir/sofosbuvir regimen also appeared to be better tolerated.

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daclatasvir (Daklinza) and sofosbuvir (Sovaldi) in patients with HCV genotype 3

ALLY-3: A phase 3, open-label trial conducted in patients with HCV genotype 3 infection evaluated the 12-week regimen of daclatasvir 60 mg plus sofosbuvir 400 mg in treatment-naïve (n=101) or treatment-experienced (n=51) patients.[221] Overall, 21% of patients had cirrhosis (treatment-naïve: 19%; treatment-experienced: 25%). Co-primary endpoints were the proportions of treatment-naïve and treatment-experienced patients achieving a SVR12. SVR12 rates were 90% in treatment-naïve patients (98% non-cirrhosis and 58% with cirrhosis) and 86% in treatment-experienced patients (92% non-cirrhosis and 69% with cirrhosis), respectively. Overall, SVR12 rates were higher in patients without cirrhosis (96%) than in those with cirrhosis (63%). SVR12 was achieved by 25 of 31 patients with previous relapse and by all 7 null responders, 2 partial responders, and 2 patients who experienced virologic breakthrough. Of whom, 5 of 7 patients previously failed treatment with a sofosbuvir-containing regimen, 2 patients previously failed telaprevir-containing regimens, and 2 patients previously failed alisporivir-containing regimens. Daclatasvir and sofosbuvir were well tolerated; there were no deaths or adverse events leading to discontinuation. The most common adverse events (in >10% of patients) were headache, fatigue, and nausea, and the incidence of grade 3 adverse events was low (2%), with no grade 4 adverse events reported.

daclatasvir (Daklinza) and sofosbuvir (Sovaldi) with or without ribavirin in patients with HCV genotypes 1 through 3

An open-label trial evaluated the efficacy of daclatasvir and sofosbuvir, with or without ribavirin, in genotype 1 through 3 HCV patients (n=211).[222] Patients were randomized 1:1:1 to sofosbuvir for 1 week, then daclatasvir plus sofosbuvir for 23 weeks, daclatasvir plus sofosbuvir for 24 weeks, or daclatasvir plus sofosbuvir with ribavirin for 24 weeks. All patients with genotype 2 and 3 were treatment-naïve (n=44), while genotype 1 patients were both treatment-naïve (n=126) and treatment-experienced (n=41). The primary efficacy outcome was SVR12. After 12 weeks of treatment, 98% of treatment-experienced genotype 1 patients, 98% of treatment-naïve genotype 1 patients, 92% of genotype 2, and 89% of genotype 3 met SVR12. Adverse effects reported most commonly included fatigue, headache, and nausea.

daclatasvir (Daklinza) and sofosbuvir (Sovaldi) in patients with HCV genotypes 1 through 4 and HIV coinfection

ALLY-2: An open-label trial in patients with HCV (genotypes 1 through 4)/HIV coinfection evaluated the efficacy of daclatasvir and sofosbuvir.[223] Treatment-naïve patients (n=151) were randomized 2:1 to daclatasvir 60 mg (dose adjusted for drug interactions) and sofosbuvir 400 mg orally daily for either 8 or 12 weeks. Treatment-experienced patients (n=52) were assigned to the 12-week regimen. While genotypes 1 through 4 were included, the primary efficacy endpoint was SVR12 in treatment-naïve genotype 1 patients, which was 83% of the population evaluated. SVR12 in treatment-naïve genotype 1 patients was 96.4% (95% CI, 89.8 to 99.2) in the 12-week group and 75.6% (95% CI, 59.7 to 87.6) in the 8-week group. In treatment-experienced patients, the SVR12 was 97.7% (95% CI, 88 to 99.9). Across all genotypes, SVR12 was 97% (95% CI, 91.6 to 99.4) and 76% (95% CI, 61.8 to 86.9) in the 12- and 8-week groups, respectively, and SVR12 was 98.1% (95% CI, 89.7 to 100) in treatment-experienced patients. HIV-1 suppression was unaffected in participants.

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daclatasvir (Daklinza) and sofosbuvir (Sovaldi) with ribavirin in patients with HCV genotypes 1, 2, 3, 4, and 6 and cirrhosis or post-liver transplantation recurrence

ALLY-1: The safety and efficacy of daily daclatasvir (60 mg/day) and sofosbuvir (400 mg/day) with ribavirin (600 mg/day) were evaluated in a multicenter, 12-week, open-label trial with a 24-week follow up in 2 cohorts of patients with HCV (any genotype, although no patients with genotype 5 were enrolled): (1) compensated or decompensated cirrhosis (n=60) and (2) post-transplantation recurrence (within 3 months of screening; n=53).[224] Patients with on-treatment transplantation were eligible to receive an additional 12 weeks of treatment following transplantation. Most patients were Caucasian (95% to 96%). Of the 113 patients enrolled, 58% of subjects had HCV genotype 1a, 19% had HCV genotype 1b, 4% had genotype 2, 15% had genotype 3, 4% had genotype 4, and 1% had genotype 6. Fifty-eight percent and 60% of patients were treatment-experienced in the post-transplant and the cirrhosis group, respectively. In the cirrhosis group, 20%, 53%, and 27% met criteria for Child-Pugh A, B, and C, respectively. The primary outcome was SVR12 in genotype 1 patients in both groups. In genotype 1 patients with cirrhosis, 82% (95% CI, 67.9 to 92) achieved SVR12. SVR12 rates in genotypes 2, 3, and 4 were 80%, 83%, and 100%, respectively (CI not provided). This cohort did not include patients with genotype 6. SVR12 was higher in patients with Child-Pugh A and B (93%) than Child-Pugh C (56%; CI not provided). SVR12 was achieved by 95% (95% CI, 83.5 to 99.4) and 91% (CI not provided) of post-transplant patients with genotypes 1 and 3, respectively. SVR12 was also achieved by the single patient with genotype 6 included in this cohort; no patients with genotypes 2 or 4 were included in this cohort. The most common adverse effects (>10% of patients) reported were headache, fatigue, anemia, diarrhea, nausea, and arthralgia, with no deaths reported to be related to treatment. Two patients in both the cirrhosis group and transplant group experienced a grade 3-4 adverse effect (anemia and non-cardiac chest pain; arthralgia and headache).

elbasvir/grazoprevir (Zepatier) in genotypes 1 and 4

The efficacy of grazoprevir/elbasvir in treatment-naïve patients with genotype 1 chronic HCV with or without cirrhosis was demonstrated in the C-EDGE TN (n=382) and C-EDGE COINFECTION (n=189) trials.[225,226] Grazoprevir/elbasvir was administered orally once daily in these trials. C-EDGE TN was a phase 3, randomized, double-blind, placebo-controlled trial in treatment-naïve patients with genotype 1 or 4 infection with or without cirrhosis. Subjects received grazoprevir/elbasvir for 12 weeks. Among patients with genotype 1 infection, 55% had genotype 1a and 45% had genotype 1b. SVR was the primary endpoint in all trials and was defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after the cessation of treatment (SVR12). Overall, SVR12 was achieved in 95% of patients following 12 weeks of treatment, 92% in genotype 1a, 98% in genotype 1b, 94% in the non-cirrhotic patients, and 97% in the cirrhotic patients. C-EDGE COINFECTION was an open-label, single-arm trial in treatment-naïve HCV/HIV-1 coinfected patients with genotype 1 or 4 infection with or without cirrhosis. Subjects received grazoprevir/elbasvir for 12 weeks. Among subjects with genotype 1 infection, 76% had genotype 1a, 23% had genotype 1b, and 1% had genotype 1-other chronic HCV infection. Overall, SVR12 was achieved in 95% of patients following 12 weeks of treatment, 94% in genotype 1a, 96% in genotype 1b, 94% in the non-cirrhotic patients, and 100% in the cirrhotic patients.

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The efficacy of grazoprevir/elbasvir in treatment-experienced patients who failed prior pegylated-interferon (PegIFN) with RBV therapy with genotype 1 chronic HCV with or without cirrhosis was demonstrated in the C-EDGE TE (n=377).[227] C-EDGE TE was a randomized, open-label comparative trial in subjects with genotype 1 or 4 infection, with or without cirrhosis, with or without HCV/HIV-1 co-infection, who had failed prior therapy with PegIFN + RBV therapy. Subjects were randomized in a 1:1:1:1 ratio to 1 of the following treatment groups: grazoprevir/elbasvir for 12 weeks, grazoprevir/elbasvir for 16 weeks, grazoprevir/elbasvir plus RBV for 12 weeks, or grazoprevir/elbasvir plus RBV for 16 weeks. Grazoprevir/elbasvir was administered orally once daily and the RBV dosage was weight-based and administered orally in 2 divided doses with food. SVR was the primary endpoint. SVR12 was achieved in 94% of patients following 12 weeks of treatment and 97% following 16 weeks of treatment. An SVR12 rate of 90% was achieved in patients with genotype 1a and 100% in patients with genotype 1b treated for 12 weeks. An SVR12 rate of 95% was achieved in patients with genotype 1a and 100% in patients with genotype 1b treated for 16 weeks.

The efficacy of grazoprevir/elbasvir in patients with genotype 4 chronic HCV infection was demonstrated in the C-EDGE trial described above (C-EDGE TN [n=26], C-EDGE COINFECTION [n=28], and C-EDGE TE [n=37]) and C-SCAPE (n=20).[228] C-SCAPE was a randomized, open-label trial of genotype 4 patients without cirrhosis in which patients were randomized in a 1:1 ratio to elbasvir/grazoprevir once daily for 12 weeks with or without ribavirin. Grazoprevir/elbasvir was administered orally once daily and the RBV dosage was weight-based and administered orally in 2 divided doses with food. SVR was the primary endpoint. In C-SCAPE, C-EDGE TN, and C-EDGE COINFECTION trials combined, 64% were treatment-naïve; 22% had cirrhosis; and 30% had HCV/HIV-1 co-infection. The SVR12 rate among subjects treated with grazoprevir/elbasvir for 12 weeks was 97%. In C-EDGE TE, a total of 37 genotype 4 treatment-experienced subjects received a 12- or 16-week grazoprevir/elbasvir with or without RBV regimen. The SVR12 rate among randomized patients treated with grazoprevir/elbasvir + RBV for 16 weeks was 100%.

elbasvir/grazoprevir (Zepatier) in treatment-experienced patients, including a protease inhibitor, with genotype 1 infection

The efficacy of grazoprevir/elbasvir in treatment-experienced patients who failed prior PegIFN with RBV and a protease inhibitor therapy with genotype 1 chronic HCV with or without cirrhosis was demonstrated in the C-SALVAGE (n=79).[229] C-SALVAGE was an open-label single-arm trial in subjects with genotype 1 infection, with or without cirrhosis, who had failed prior treatment with boceprevir, simeprevir, or telaprevir in combination with PegIFN + RBV. Subjects received grazoprevir/elbasvir + RBV for 12 weeks. Grazoprevir/elbasvir was administered orally once daily and the RBV dosage was weight-based and administered orally in 2 divided doses with food. SVR was the primary endpoint. Among these subjects, 43% had cirrhosis and 46% had baseline NS3 resistance-associated substitutions. Overall, SVR12 was achieved in 96% of subjects. Treatment outcomes were consistent in genotype 1a and genotype 1b subjects, in subjects with different response to previous HCV therapy, and in subjects with or without cirrhosis. Treatment outcomes were generally consistent in subjects with or without NS3 resistance-associated substitutions at baseline, although limited data are available for subjects with specific NS3 resistance-associated substitutions.

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elbasvir/grazoprevir (Zepatier) in genotype 1 infection with severe renal impairment

The efficacy of grazoprevir/elbasvir in patients with genotype 1 HCV and severe renal impairment, including those on hemodialysis, was demonstrated in the C-SURFER (n=235).[230,231] C-SURFER was a randomized, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with chronic kidney disease (CKD) Stage 4 (eGFR 15 to 29 mL/min/1.73 m^2) or CKD Stage 5 (eGFR < 15 mL/min/1.73 m^2), including subjects on hemodialysis, who were treatment-naïve or who had failed prior therapy with IFN or PegIFN ± RBV therapy. Subjects were randomized in a 1:1 ratio to 1 of the following treatment groups: grazoprevir/elbasvir for 12 weeks (treatment group) or placebo for 12 weeks. Overall, an SVR12 was achieved in 94% of patients, 97% in genotype 1a, 92% in genotype 1b, 93% in dialysis patients, and 100% and 93% in patients with CKD stages 4 and 5, respectively.

ledipasvir/sofosbuvir (Harvoni) in genotype 1 infection

ION-1: This was a phase 3, randomized, open-label, multicenter trial involving previously untreated patients (n=865) with chronic HCV genotype 1 infection.[232] Patients were randomly assigned in a 1:1:1:1 ratio to receive a fixed-dose combination tablet containing 90 mg of ledipasvir and 400 mg of sofosbuvir once daily for 12 weeks or 24 weeks with or without twice-daily ribavirin, for both treatment durations. Randomization was stratified according to HCV subtype (1a or 1b) and the presence or absence of cirrhosis. The presence of cirrhosis was defined as a liver-biopsy specimen showing evidence of cirrhosis (Metavir stage F4) or Ishak score of 5 or 6, a FibroScan score of more than 12.5kPa or a FibroTest score of more than 0.75 and an aspartate aminotransferase: platelet ratio index of more than 2. Overall, 16% of the 865 patients who received treatment in this trial had cirrhosis. The primary efficacy endpoint was SVR at 12 weeks. The SVR rates for the 4 groups were 99% (95% CI, 96 to 100) for the 12 weeks of ledipasvir/sofosbuvir, 97% (95% CI, 94 to 99) for the 12 weeks of ledipasvir/sofosbuvir plus ribavirin, 98% (95% CI, 95 to 99) for the 24 weeks of ledipasvir/sofosbuvir, and 99% (95% CI, 97 to 100) for the 24 weeks of ledipasvir/sofosbuvir plus ribavirin. The SVR rates for all 4 treatment groups were statistically superior to the calculated historical SVR rate of 60% in this patient population (p<0.001 for all comparisons). The SVR ranged from 94% to 100% in patients with cirrhosis, from 97% to 99% in patients with HCV genotype 1a infection, 97% to 99% among those with a non-CC *IL28B* allele, and 91% to 100% among African American patients. A total of 10 patients in the two 24-week groups discontinued treatment prematurely due to adverse events and all 10 of these patients had a SVR; the shortest duration of therapy among these patients was 8 weeks. No patient in the 12-week groups discontinued treatment early. Serious adverse events included cellulitis, chest pain, gastroenteritis, hand fracture, noncardiac chest pain, and pneumonia; each of these occurred in 2 patients. The most common mild to moderate adverse events were fatigue, nausea, headache, and insomnia. The authors concluded the addition of ribavirin did not improve treatment outcomes and the rates of treatment discontinuation were higher in the groups treated for 24 weeks than in the groups treated for 12 weeks. Based on these findings, the regimen of 12 weeks of ledipasvir/ribavirin without ribavirin constitutes an effective treatment for previously untreated patients with HCV genotype 1 infection with or without cirrhosis and is associated with the lowest rate of adverse events of the 4 regimens evaluated.

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ION-2: This was a phase 3, randomized, open-label, multicenter study involving patients (n=440) infected with chronic HCV genotype 1 who had not had a SVR after treatment with peginterferon and ribavirin, with or without a protease inhibitor.[233] The 1:1:1:1 randomization arms were identical to ION-1 with 4 total groups, two 12-week treatment groups, 1 with and 1 without added ribavirin and two 24-week treatment groups, 1 with and 1 without added ribavirin. Patients were stratified according to genotype (1a versus 1b), presence or absence of cirrhosis, and response to prior therapy (relapse or virologic breakthrough versus no response). These stratification groups were generally balanced among the 4 treatment arms. Overall, 52% of the enrolled patients had received prior treatment with a protease inhibitor regimen and 88% had the non-CC *IL28B* genotype. The primary efficacy endpoint was SVR12 with a secondary endpoint of SVR24. The SVR rates for the 4 groups were 94% (95% CI, 87 to 97), for the 12 weeks of ledipasvir/sofosbuvir, 96% (95% CI, 91 to 99) for the 12 weeks of ledipasvir/sofosbuvir plus ribavirin, 99% (95% CI, 95 to 100) for the 24 weeks of ledipasvir/sofosbuvir, and 99% (95% CI, 95 to 100) for the for the 24 weeks of ledipasvir/sofosbuvir plus ribavirin. The sustained virologic response was superior to the adjusted historical response rate of 25% in this patient population (p<0.001 for all comparisons). A total of 11 patients who were on 1 of the 12-week treatment arms experienced virologic relapse. No patient in the group that received 24 weeks of treatment had a virologic relapse. All patients who had achieved an SVR12 also had an SVR24; no patient had a relapse after post-treatment week 12. The response rates were similar among patients with genotype 1a and those with genotype 1b infection, among patients who had previously received peginterferon and ribavirin and those who had received a protease inhibitor regimen, and among those patients with no response to prior treatment and those with prior virologic breakthrough or relapse. Ribavirin had no effect on response rates, regardless of treatment duration. Patients with cirrhosis who received the 12-week regimen, with or without ribavirin, had a SVR rate of 86% and 82%, respectively. The SVR rates for cirrhotic patients randomized to the two 24-week arms were 95% and 100%. The difference between the response rate among patients with cirrhosis who received 12 weeks of treatment and the rates among patients with cirrhosis who received 24 weeks of treatment was significant (p=0.007). The multivariate exact logistic-regression analysis identified the absence of cirrhosis as the only baseline factor associated with a significant increase in the rate of response. None of the patients in the study discontinued treatment prematurely due to adverse effects. No serious adverse events occurred in patients who received either 12-week regimen, whereas, 6% of patients who received a 24-week therapy experienced a serious adverse event. These serious adverse effects included 1 patient each with hepatic encephalopathy, intervertebral disk protrusion, noncardiac chest pain, spondylolisthesis, convulsion, upper gastrointestinal hemorrhage, and unstable angina. Overall, the rate of adverse events was substantially lower in the group that received 12 weeks of ledipasvir/sofosbuvir alone (67%) than in the other 3 treatment groups (81% to 90%). Higher rates of constitutional and neuropsychiatric side effects were observed in the 2 groups that received the ribavirin-containing regimen than in the 2 groups that received ledipasvir-sofosbuvir alone.

ION-3: This was a phase 3, randomized, open-label, multicenter trial enrolling previously untreated patients (n=647) with HCV genotype 1 infection without cirrhosis to receive ledipasvir/sofosbuvir for 8 weeks, ledipasvir/sofosbuvir plus ribavirin for 8 weeks, or ledipasvir/sofosbuvir for 12 weeks.[234] Patients were randomized 1:1:1 into these groups and stratified by HCV genotype (1a or 1b). The goal of the trial was to establish the feasibility of shortening the treatment duration for this select group of patients and the primary endpoint was SVR12 as compared to the historical control rate of 60% in this population. A key secondary endpoint was the noninferiority of 8 weeks of ledipasvir/sofosbuvir to the

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other treatment regimens. Patients eligible for this trial were required to have a HCV RNA level of at least 10^4 IU/mL, alanine and aspartate aminotransferase levels of no more than 10 times the upper limit of normal, a platelet count of more than 90,000 per cubic millimeter, and hemoglobin of at least 11 g/dL in women or at least 12 g/dL in men. The primary endpoint was met in all 3 treatment groups, with SVR rates superior to the adjusted historical control rate of 60% ($p<0.001$ for all comparisons). The 8-week ledipasvir/sofosbuvir treatment arm had a 94% SVR12 rate (95% CI, 90 to 97), the ledipasvir/sofosbuvir/ribavirin 8-week treatment arm had a 93% SVR12 rate (95% CI, 89 to 96), and the 12-week ledipasvir/sofosbuvir arm has a 95% SVR 12 rate (95% CI, 92 to 98). In the secondary analysis of noninferiority, the rate of sustained virologic response among patients who received 8 weeks of ledipasvir/sofosbuvir without ribavirin met the prespecified criteria for noninferiority compared to the response rates in the other 2 treatment groups. Patients with characteristics historically associated with a poor response to interferon-based treatment including non-CC *IL28B* genotype, high viral load at baseline, black race, and HCV genotype 1a infection, had SVR12 rates similar to the rates among patients without these characteristics. The rates of response to 8 weeks of ledipasvir/sofosbuvir ranged from 89% to 100% in all these subgroups. The baseline fibrosis score also had no discernible effect on the SVR12 rate. Five percent of patients in the 8-week ledipasvir/sofosbuvir group experienced a virologic relapse after the end of therapy, as did 4% in the 8-week ledipasvir/sofosbuvir/ribavirin group and 1% in the 12-week group. Fatigue, headache, and nausea were the most common adverse events. Although relapse was more common among patients who received 8 weeks of treatment than those who received 12 weeks of treatment, the small numbers of patients who had a relapse were not sufficient to identify baseline characteristics or response variables during treatment that were associated with relapse. Overall, this study supports the efficacy of an 8-week course of ledipasvir/sofosbuvir across a broad range of previously untreated patients with HCV genotype 1 infection without cirrhosis; however, this regimen has not been evaluated in patients with cirrhosis.

ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) plus ribavirin versus placebo in genotype 1

SAPPHIRE-I was an international phase 3, randomized, double-blind, placebo-controlled trial involving 631 previously untreated patients with HCV genotype 1 infection.[235] Patients were randomized to active treatment with ABT-450/r (150 mg/100 mg)-ombitasvir (25 mg), dasabuvir (250 mg twice daily) and ribavirin (weight-based dosing), or matching placebos for 12 weeks. Randomization was stratified by HCV genotype (1a or non-1a) and IL28B genotype (CC or non-CC). (After the double-blind period, patients randomized to placebo received the active regimen as open-label therapy for 12 additional weeks). The primary endpoint was SVR12 (HCV RNA < 25 IU/mL at 12 weeks after the end of treatment). The SVR12 of the active treatment group was compared to a historical response rate of 78% in previously untreated patients without cirrhosis who received telaprevir/peginterferon/ribavirin. The SVR12 of the active treatment group was 96.2% (95% CI, 94.5 to 97.9), which was statistically superior to the historical control. The response rates were 95.3% among patients with HCV genotype 1a and 98% among patients with HCV genotype 1b infections. The SVR12 rates were similar regardless of baseline fibrosis score (97% for F0/F1, 94.3% for F2, and 92.5% for F3). One patient in the active treatment group had virologic failure during the double-blind treatment period and 7 active treatment patients (1.5%) had a relapse by post-treatment week 12. Each of these 8 patients had at least 1 amino acid variant known to confer resistance to 1 of the 3 direct acting antiviral agents

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included in the regimen. Modifications of the ribavirin dose due to adverse events occurred in 26 patients. The SVR 12 was 93.5% among patients who had a modification of the ribavirin dose and 96.4% among those who did not have a ribavirin dose modification. Nausea, pruritus, insomnia, diarrhea, and asthenia occurred in significantly more patients receiving active treatment compared to patients receiving placebo ($p<0.05$ for all comparisons).

ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) plus ribavirin in genotype 1 patients with previous treatment experience

SAPPHIRE-II was an international, randomized, placebo-controlled, double-blind, phase 3 trial with an identical study design to SAPPHIRE-I but enrolled patients (n=394) who had previously been treated with peginterferon-ribavirin (PEG/RBV) and had a partial response or a null response or had experienced a relapse.[236] All patients had HCV genotype 1 and no cirrhosis. Patients were excluded if they did not have a response to prior triple therapy including a protease inhibitor. Patients with Metavir scores of 3 or above were also excluded. The historical response rate for this group of patients was determined to be 65% based on a retreatment regimen of peginterferon-ribavirin and telaprevir. The SVR12 for the active treatment group in this trial was 96.3% (95% CI, 94.2 to 98.4), superior to the historical control rate. Response rates of 95.3%, 100%, and 95.2% were seen in patients with a prior relapse, a prior partial response, and a prior null response, respectively. The 2 most common adverse events in both the active treatment group and the placebo group were headache and fatigue. Only pruritus occurred more frequently in the active regimen group compared to placebo (13.8% versus 5.2%; $p=0.03$). A total of 2.4% of patients who completed therapy had a post-treatment viral relapse.

ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) with or without ribavirin in genotype 1

PEARL II was a multicenter, open-label, phase 3 trial designed to answer the question of whether ribavirin is necessary in the ombitasvir/paritaprevir/ritonavir plus dasabuvir regimen in the treatment of patients with HCV genotype 1b without cirrhosis who had previously been treated with peginterferon and ribavirin (PEG/RBV).[237] Patients (n=186) were randomized to identical regimens of co-formulated ombitasvir/paritaprevir/ritonavir (150 mg/100 mg/25 mg) and dasabuvir (250 mg twice daily), with or without ribavirin (weight-based dosing), for 12 weeks. Previous null responders, partial responders, and relapsers were evenly stratified between the 2 treatment arms. The primary endpoint was SVR12, which was compared to a historical response rate of 64% in this patient population treated with peginterferon, ribavirin, and telaprevir. Hemoglobin levels less than the lower limit of normal at the end of treatment was a secondary endpoint. The SVR12 rate for the group of patients who received ribavirin was 96.6% (95% CI, 92.8 to 100) and 100% for the group of patients who did not receive ribavirin (95% CI, 95.9 to 100). The rate of response in the group who did not receive ribavirin was non-inferior to the group who did receive ribavirin and both groups were non-inferior to the historical response rate. In the group of patients receiving ribavirin, SVR12 rates were 93.5%, 96%, and 100% in prior null responders, partial responders, and relapsed patients, respectively. SVR12 rates were 100% in all subgroups of the ribavirin-free arm. The most common adverse events in both groups were fatigue (31.9% and 15.8%) and headache (24.2% and 23.2%) in the ribavirin and non-ribavirin groups, respectively. Patients receiving ribavirin also experienced statistically significantly more events of insomnia, anemia, rash, and increased bilirubin levels. Hemoglobin levels less than the lower limit of

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normal at the end of treatment was experienced more often by patients receiving ribavirin than those who did not receive ribavirin (42% versus 5.5%, respectively; p<0.001).

Two phase 3, double-blind, randomized, placebo-controlled trials were designed to evaluate the role of ribavirin in treatment-naive HCV genotype 1 patients without cirrhosis (PEARL-III and PEARL-IV).[238] The safety and efficacy of a 12-week treatment regimen of co-formulated ABT-450/r-ombitasvir (150 mg/100 mg/25 mg) and dasabuvir (250 mg twice daily), with or without ribavirin (weight-based dosing), were examined in previously untreated patients without cirrhosis who had HCV genotype 1a (PEARL-IV) or HCV genotype 1b (PEARL-III). Patients in both trials received identical open-label regimens of ABT-450/r-ombitasvir and dasabuvir along with either ribavirin or placebo. In PEARL-III, 419 patients underwent randomization and, in PEARL-IV, 305 patients underwent randomization. SVR12 was the primary endpoint for all analyzed groups and the primary objective of both studies was to assess the noninferiority of all groups compared to a corresponding historical rate (72% for HCV genotype 1a and 80% for HCV genotype 1b). Secondary efficacy objectives in each study were to assess the noninferiority of the SVR12 rate in the group that did not receive ribavirin as compared with the group that did receive ribavirin. Other objectives included assessing the percentage of patients in each group with a hemoglobin level below the lower limit of normal at the end of treatment and the percentage of patients in each group with virologic failure during treatment or relapse after treatment. For patients with HCV genotype 1b (PEARL-III), 99.5% (95% CI, 98.6 to 100) of patients receiving ribavirin achieved an SVR12 and 99% (95 % CI, 97.7 to 100) of patients who did not receive ribavirin achieved an SVR12. Among the patients with HCV genotype 1a (PEARL-IV), 97% (95% CI, 93.7 to 100) of patients receiving ribavirin achieved an SVR12 and 90.2% (95% CI, 86.2 to 94.3) of patients who did not receive ribavirin achieved an SVR12.

The SVR12 rates for both genotype 1a regimens (with or without ribavirin) were non-inferior and superior to the historical rate; however, the regimen without ribavirin for genotype 1a patients did not meet the non-inferiority criteria as compared to the regimen with ribavirin and there was a statistically significant difference between these 2 groups (95% CI, -12 to -1.5). The rate of virologic failure was higher in the HCV genotype 1a patients who did not receive ribavirin (7.8%) compared to the HCV genotype 1a group who did receive ribavirin (2%). A total of 18 patients with genotype 1a infection had virologic failure, 16 of whom received the regimen without ribavirin. For genotype 1b patients, the SVR12 rates among patients who received ribavirin and those who did not were both non-inferior and superior to the historical control. In addition, the SVR12 rate among patients who did not receive ribavirin was non-inferior to the rate among those who received ribavirin (difference -0.5 percentage points [95% CI, -2.1 to 1.1] for genotype 1b patients. In both studies, adverse events were more frequently reported in the groups receiving antiviral regimens that contained ribavirin than in groups that received the ribavirin-free regimen (p=0.03 in the genotype 1a study and p=0.003 in the genotype 1b study). The most common adverse events reported in the 2 studies, headache and fatigue, did not differ significantly in either study between the group that received ribavirin and the group that did not receive it. Pruritus, nausea, and insomnia all occurred at a higher frequency among patients who received ribavirin than among those who did not. In the genotype 1a study, 42% of patients treated with ribavirin had a hemoglobin level below the lower limit of normal at the end of treatment compared to only 3.9% of patients who received the ribavirin-free regimen (p<0.001). Similarly, in the genotype 1b study, 51.2% of patients who received ribavirin had a low hemoglobin level at the end of treatment as compared with 3.4% of patients who did not receive ribavirin (p<0.001).

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ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) plus ribavirin in genotype 1 patients with compensated cirrhosis

TURQUOISE-II was a randomized, open-label, international phase 3 trial enrolling both untreated and previously treated adults (n=380) with HCV genotype 1 infection and compensated cirrhosis (CC).[239] Eligible patients had documentation of liver cirrhosis, as well as a plasma HCV RNA level of more than 10,000 IU/mL. Patients enrolled in the trial also were required to have a baseline platelet count of at least 60,000 mm^3, a serum albumin of ≥ 2.8 g/dL, a total bilirubin < 3 g/dL, an INR of 2.3 or less, and a serum alpha-fetoprotein level of 100 ng/mL or less. Patients who had previously received telaprevir or boceprevir were excluded from the study, as were patients with a diagnosis of hepatocellular carcinoma. All patients received ABT-450 with ritonavir (ABT-450/r) at a dose of 150 mg of ABT-450 and 100 mg of ritonavir and ombitasvir 25 mg co-formulated into 1 tablet once daily along with dasabuvir 250 mg twice daily and ribavirin administered at 1,000 mg or 1,200 mg twice daily according to body weight. Patients were randomized to either 12 weeks of therapy or 24 weeks of therapy. Patients were stratified according to HCV subgenotype (1a or 1b), IL28B genotype (CC versus non-CC) and whether or not they had failed previous PEG/RBV as well as the type of failure (null response, partial response, or relapse). The primary efficacy endpoint was SVR12 compared to a historical rate of 47% (95% CI, 41 to 54) with a regimen of peginterferon/ribavirin/telaprevir in this patient population. A total of 191 of 208, or 91.8%, (97.5% CI, 87.6 to 96.1) of patients who were randomized to 12 weeks of treatment achieved a SVR12, while 95.9% (97.5% CI, 92.6 to 99.3) of patients who were randomized to 24 weeks of treatment achieved a SVR12. In both treatment groups and across the randomization strata, the primary endpoint of superiority compared to the historical SVR12 rate with telaprevir-based regimens was achieved. The difference in SVR12 between the 12-week treatment group and the 24-week treatment group was not significant (p=0.09); however, a multivariate logistic-regression analysis indicated that a prior null response to peginterferon-ribavirin, infection with HCV subgenotype 1a, and former injection-drug use were associated with a lower likelihood of achieving a SVR12. This population had an SVR12 rate of 80% in the 12-week arm and 92.9% in the 24-week arm. When examining virologic failure during treatment or relapse after treatment, significantly more patients in the 12-week group than in the 24-week group had a relapse (5.9% [95 % CI, 2.7 to 9.2] versus 0.6% [95% CI, 0 to 1.8]). More than half of the relapses in the 12-week group occurred in patients with HCV genotype 1a and a prior null response to peginterferon-ribavirin treatment. The majority of adverse events were mild or moderate in severity. Two percent of patients in either randomized group discontinued the study drug due to an adverse event. The most frequent grade 3 laboratory abnormality was elevated total bilirubin levels. There were 34 patients who required a reduction in the ribavirin dose due to anemia; all 34 of those patients achieved a SVR12.

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ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) plus ribavirin in HCV/HIV co-infected patients with genotype 1

TURQUOISE-I was an open-label clinical trial involving 63 patients with HCV/HIV co-infection.[240] Patients in this trial were treated for 12 or 24 weeks with Viekira Pak in combination with ribavirin and were on a stable HIV antiretroviral therapy regimen. Antiretroviral medications were adjusted according to protocol stipulations depending on the drug regimen. Of the patients enrolled in the trial, 67% were HCV treatment-naïve and 19% had compensated cirrhosis and 89% had HCV genotype 1a infection. The SVR12 rates were 91% (51/56 patients) in those patients with HCV genotype 1a infection and 100% (7/7) for patients with HCB genotype 1b infection. One patient had confirmed HIV-1 RNA > 400 copies/mL during the post-treatment period but had no evidence of resistance to the antiretroviral drug regimen. No subjects switched their antiretroviral regimen due to loss of plasma HIV-1 RNA suppression.

ombitasvir/paritaprevir/ritonavir (Technivie) plus ribavirin in genotype 4

The efficacy and safety of Technivie were evaluated in a single clinical trial in patients with genotype 4 chronic HCV.[241] PEARL-I was a randomized, global, multicenter, open-label trial that enrolled 135 adults with HCV genotype 4 infection without cirrhosis who were either treatment-naïve or did not achieve a virologic response with prior treatment with pegylated interferon + ribavirin (PEG/RBV). Previous exposure to HCV direct-acting antivirals was prohibited. Treatment-naïve patients were randomized in a 1:1 ratio to receive 1 ombitasvir 25 mg tablet, 3 paritaprevir 50 mg tablets, and 1 ritonavir 100 mg capsule once-daily with food in combination with ribavirin (n=42) or without ribavirin (n=44) for 12 weeks. PEG/RBV treatment-experienced subjects received 1 ombitasvir 25 mg tablet, 3 paritaprevir 50 mg tablets, and 1 ritonavir 100 mg capsule once daily with food in combination with ribavirin for 12 weeks (49 patients). The ribavirin dosage was 1,000 mg per day for patients weighing less than 75 kg or 1,200 mg per day for subjects weighing greater than or equal to 75 kg. The primary endpoint was sustained virologic response defined as HCV-RNA below the lower limit of quantification (<LLOQ) 12 weeks after the end of treatment (SVR12) using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System, which has an LLOQ of 25 IU per mL. All 42 of the treatment-naïve patients taking ombitasvir + paritaprevir + ritonavir with ribavirin for 12 weeks achieved an SVR12 (100%). All 49 of the treatment-experienced patients taking ombitasvir + paritaprevir + ritonavir with ribavirin for 12 weeks achieved an SVR12 (100%). Out of the 44 treatment-naïve patients taking ombitasvir + paritaprevir + ritonavir without ribavirin, 40 patients achieved an SVR12 (91%). Of the 129 patients that achieved an SVR12, all 129 maintained their response 24 weeks after the end of treatment (SVR24).

AGATE-I: The efficacy and safety of Technivie in treatment-naïve and treatment-experienced genotype 4 patients with cirrhosis were evaluated in a phase 3, multinational, multicenter, open-label trial.[242] A total of 120 patients were enrolled and randomized to receive treatment with ombitasvir, paritaprevir, and ritonavir plus ribavirin for either 12 weeks (n=59) or 16 weeks (n=61). The primary outcome was the proportion of patients with an SVR12 in the intention-to-treat population, with the lower 97.5% confidence interval compared with a clinically relevant threshold (67%; based on SVR reported for pegylated interferon and ribavirin) to achieve superiority. A SVR12 was achieved in 97% (57 of 59 patients) in the 12-week group (97.5% CI, 86.7 to 99.2), and in 98% (60 of 61 patients) in the 16-week group (97.5% CI, 89.6 to 99.8). In the 12-week group, 1 patient experienced virological breakthrough and 1 patient discontinued prematurely after the first day of treatment. In the 16-week group, 1

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patient missed the post-treatment week 12 visit. Adverse events that occurred in at least 10% of all patients in the 12-week and 16-week groups, respectively, include asthenia (18%, 32%), fatigue (17%, 33%), headache (23%, 23%), anemia (15%, 20%), pruritus (8%, 23%), nausea (10%, 13%), and dizziness (7%, 15%).

sofosbuvir/velpatasvir (Epclusa) in genotypes 1, 2, 4, 5, and 6

ASTRAL-1: This randomized double-blind trial evaluated the efficacy of sofosbuvir/velpatasvir in treatment-naïve and treatment-experienced (prior interferon-containing regimen) patients (n=740) with genotype 1, 2, 4, 5, or 6 without cirrhosis or with compensated cirrhosis (Child-Pugh A).[243] Patients were randomized 5:1 to either sofosbuvir/velpatasvir 400/100 mg or placebo once daily for 12 weeks; however, all patients with genotype 5 were assigned sofosbuvir/velpatasvir due to the low prevalence of this genotype. In this trial, randomization was stratified according to the genotype and the presence or absence of cirrhosis. In the sofosbuvir/velpatasvir group (n=624), 34% of the patients had HCV genotype 1a, 19% genotype 1b, 17% genotype 2, 19% genotype 4, 6% genotype 5, and 7% genotype 6. Nineteen percent of the patients assigned sofosbuvir/velpatasvir had cirrhosis. The primary efficacy endpoint was the rate SVR12. Overall, SVR12 among patients who received 12 weeks of sofosbuvir/velpatasvir was 99% (95% CI, 98 to > 99), which was significantly superior to the prespecified performance goal of 85% ($p<0.0001$). None of the 116 patients in the placebo group had a SVR. Rates of SVR were similar regardless of the HCV genotype: 98% in patients with genotype 1a infection, 99% with genotype 1b, 100% with genotype 2, 100% with genotype 4, 97% with genotype 5, and 100% with genotype 6. Nearly all of the patients with cirrhosis achieved SVR12 (all genotypes; 120/121; 99%). Only 1 of the patients in the sofosbuvir/velpatasvir group discontinued treatment prematurely because of an adverse event.

sofosbuvir/velpatasvir (Epclusa) in genotypes 2

ASTRAL-2: This open-label trial (n=266) compared sofosbuvir/velpatasvir 400/100 mg once daily (n=134) to sofosbuvir 400 mg with weight-based ribavirin for 12 weeks (n=132) in treatment-naïve and treatment-experienced (prior interferon-containing regimen) patients with genotype 2.[244] Fourteen percent of those enrolled had cirrhosis while 15% were treatment-experienced. The overall SVR12 rates in subjects who received sofosbuvir/velpatasvir and sofosbuvir with ribavirin, the primary outcome, were 99% (95% CI, 96 to 100) and 94% (95% CI, 88 to 97), respectively. There were no virologic failures among patients receiving sofosbuvir/velpatasvir despite the presence of NS5A and NS5B resistance-associated variants; however, in those receiving sofosbuvir with ribavirin, 6 patients (5%) had a virologic relapse and 2 were lost to follow-up.

sofosbuvir/velpatasvir (Epclusa) in genotypes 3

ASTRAL-3: This open-label trial (n=552) compared sofosbuvir/velpatasvir 400/100 mg once daily for 12 weeks (n=277) to sofosbuvir 400 mg with weight-based ribavirin for 24 weeks (n=275) in treatment-naïve and treatment-experienced (prior interferon-containing regimen) patients with genotype 3.[245] Thirty percent of those enrolled had cirrhosis while 26% were treatment-experienced. The SVR12 rates in patients who received sofosbuvir/velpatasvir were 95% (95% CI, 92 to 98) compared to 80% (95% CI, 75 to 85) in those who received sofosbuvir with ribavirin.

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sofosbuvir/velpatasvir (Epclusa) in genotypes 1, 2, 3, 4, and 6 with decompensated cirrhosis

ASTRAL-4: An open-label trial, evaluated the efficacy of sofosbuvir/velpatasvir in treatment-naïve and treatment-experienced patients with genotypes 1 through 6 chronic HCV infection and decompensated cirrhosis (Child-Pugh B).[246] Patients were randomized 1:1:1 to sofosbuvir/velpatasvir 400/100 mg once daily for 12 weeks, sofosbuvir/velpatasvir 400/100 mg once daily with ribavirin for 12 weeks, or sofosbuvir/velpatasvir 400/100 mg once daily for 24 weeks (n=267). Of those who received treatment, 78% were genotype 1, 4% were genotype 2, 15% were genotype 3, 3% were genotype 4, and < 1% were genotype 6; while not excluded, no genotype 5 patients were enrolled. The median baseline Child-Pugh score was 8 (range, 5 to 10) and the median baseline Model for End-Stage Liver Disease (MELD) score was 10 (range, 6 to 24; majority ≤ 15). Overall SVR12 rates, the primary outcome, were 83% (95% CI, 74 to 90), 94% (95% CI, 87 to 98), and 86% (95% CI, 77 to 92) for the 12-week regimen of sofosbuvir/velpatasvir, the 12-week regimen of sofosbuvir/velpatasvir with ribavirin, and the 24-week regimen of sofosbuvir/velpatasvir, respectively. Notably, SVR12 rates as low as 50% were reported in genotype 3 patients assigned sofosbuvir/velpatasvir for 12 or 24 weeks (no ribavirin).

SUMMARY

Therapy for chronic hepatitis C virus (HCV) has evolved substantially in the last 2 decades since interferon-alpha was first approved for this indication. Genotype 1 accounts for about 70% to 75% of the HCV cases in the United States. Historically, monotherapy with interferon resulted in sustained virologic responses (SVR) of approximately 10% to 20% in patients with genotype 1 and was associated with substantial adverse drug effects. With the introduction of pegylated interferons, which prolonged half-life and improved response rate, as well as the addition of ribavirin, the standard of care became dual therapy with peginterferon plus ribavirin. This combination resulted in SVR rates of 40% to 50% and remained the standard of care for many years; however, this regimen was not well tolerated as interferon therapy is associated with significant adverse effects, including influenza-like illness, neuropsychiatric symptoms, and ribavirin is associated with anemia. Triple therapy with the first generation protease inhibitors (no longer available), peginterferon, and ribavirin resulted in SVR rates of 60% to 80% in genotype 1 HCV patients. An additional NS3/4A protease inhibitor, simeprevir (Olysio), was approved in 2013 and carries indications for genotypes 1 and 4. Simeprevir is considered a second generation protease inhibitor. This second wave of protease inhibitors offer some advantages over the first generation NS3/4A protease inhibitors, including improved pharmacokinetics allowing once daily dosing, possible shorter treatment durations, and a more tolerable side effect profile; however, simeprevir is still associated with many drug interactions and resistance profiles. In addition, patients prescribed simeprevir in conjunction with peginterferon plus ribavirin should be screened for the commonly occurring Q80K mutation. Alternate therapy should be considered if this polymorphism is present, since simeprevir, used in combination with peginterferon plus ribavirin, has been found to be less effective in the presence of this mutation.

In December 2013, sofosbuvir (Sovaldi) was approved by the FDA with a breakthrough therapy designation. Sofosbuvir represents a new class of direct acting antivirals (DAAs) as a HCV nucleotide analog NS5B polymerase inhibitor. It is indicated as a component of a combination regimen for patients with HCV genotypes 1, 2, 3, and 4, resulting in SVR rates of approximately 90% in treatment-

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naïve patients. Sofosbuvir (Sovaldi) combined with ribavirin for the treatment of genotypes 2 and 3 represented the first all-oral regimen approved by the FDA for HCV therapy.

In 2014, FDA rulings brought about new therapies and expanded indications for previously approved medications. In October 2014, a new fixed-dose once daily oral combination tablet of ledipasvir/sofosbuvir (Harvoni) was approved for the treatment of HCV genotype 1, and its indication was expanded to include patients with genotypes 4, 5, and 6 in November 2015. This therapy combines ledipasvir, the first in a new class of DAAs classified as an HCV NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor. In November 2014, simeprevir received FDA approval for use in combination with sofosbuvir, but this oral combination is not co-formulated. In December 2014, the combination ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak) was approved for the treatment of genotype 1 patients with an extended release formulation (Viekira XR) released in July 2016. This combination includes an NS5A inhibitor (ombitasvir), an NS3A/4A protease inhibitor (paritaprevir), a non-nucleoside NS5B polymerase inhibitor (dasabuvir), and a CYP3A inhibitor (ritonavir) to boost paritaprevir pharmacologically providing increased plasma concentrations. The therapies approved in 2014 represent significant innovation in the treatment hepatitis C as these all-oral regimens have shown SVR rates of 90% or greater.

A similar agent, ombitasvir, paritaprevir, and ritonavir (Technivie) was approved in 2015 and is indicated for the treatment of genotype 4 in combination with ribavirin in patients without cirrhosis or with compensated cirrhosis and has also demonstrated SVR rates of 90% or greater in clinical trials. Daclatasvir (Daklinza), also approved in 2015, is indicated with sofosbuvir for the treatment of genotypes 1 or 3 with SVR rates of 90% or greater as well, but sustained SVR rates are reduced in patients with cirrhosis and certain genetic polymorphisms. Approved in January 2016, elbasvir/grazoprevir (Zepatier) combines a NS5A inhibitor with another NS3A/4A protease inhibitor and is indicated for genotypes 1 and 4 with or without ribavirin. Testing for NS5A resistance-associated polymorphisms is needed for patients with genotype 1a since presence may affect both treatment duration and eligibility for this regimen. In June 2016, the fixed-dose once daily pangenotypic combination of sofosbuvir/velpatasvir (Epclusa) was approved which introduced the first hepatitis C treatment with activity against all 6 genotypes.

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) has published guidance for testing, managing, and treating hepatitis C. This guidance defines recommended regimens (favored for most patients), alternative regimens (effective regimens that may be optimal for a specific patient situation, though not considered a recommended regimen for most patients due to potential disadvantages, limitations use in select populations, or less supporting data), as well as regimens that are not recommended (clearly inferior or harmful treatment options) for each genotype. The guidelines offer expanded options for patients not addressed in the current FDA labeling including patients who are interferon-ineligible, as well as patients who have not responded to previous standard therapy. The AASLD/IDSA guidelines are continually updated including consideration for advances in treatment and the availability of all-oral regimens with substantially higher SVR rates compared to preceding treatment options.

The HCV market is expected to grow, as there are more treatments in the pipeline, including additional pangenotypic treatment options.

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