



Hepatitis C Agents

Therapeutic Class Review (TCR)

January 30, 2015

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage or retrieval system without the express written consent of Provider Synergies, L.L.C.

All requests for permission should be mailed to:

Attention: Copyright Administrator
Intellectual Property Department
Provider Synergies, L.L.C.
10101 Alliance Road, Suite 201
Cincinnati, Ohio 45242

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

Drug	Mfr	FDA-Approved Indications
Interferons		
interferon alfacon-1 (Infergen®) ¹	Kadmon	<p>Chronic hepatitis C</p> <ul style="list-style-type: none"> ▪ In adults (>18 years old) with compensated liver disease and anti-HCV serum antibodies and/or HCV RNA ▪ Combination therapy with ribavirin is preferred unless a patient cannot take ribavirin <ul style="list-style-type: none"> – Safety and efficacy data are not available for use of interferon alfacon-1 with or without ribavirin for the treatment of patients co-infected with hepatitis B or HIV <p>Patients with the following characteristics are less likely to benefit from treatment of interferon alfacon-1 and ribavirin: response of <1-\log_{10} drop HCV RNA on previous treatment, genotype 1, high viral load (>850,000 IU/mL), African American race, and/or presence of cirrhosis.</p>
peginterferon alfa-2a (Pegasys®) ²	Genentech	<p>Chronic hepatitis C</p> <ul style="list-style-type: none"> ▪ Alone or in combination with ribavirin in patients \geq 5 years old with compensated liver disease who have not been previously treated with interferon alfa ▪ Includes patients with histological evidence of cirrhosis (Child-Pugh class A) and compensated liver disease ▪ Includes adult patients with clinically stable HIV disease and CD4 counts > 100 cells/mm³ ▪ In combination with ribavirin and an approved HCV NS3/4A protease inhibitor in patients \geq 18 years of age with HCV genotype 1 infection ▪ In combination with ribavirin in patients with HCV genotypes other than 1, pediatric patients (5-17 years of age), or in patients with HCV genotype 1 infection where use of an HCV NS3/4A protease inhibitor is not warranted based on tolerability, contraindications, or other clinical factors <p>Monotherapy is not recommended unless a patient has a contraindication to, or significant intolerance, to ribavirin. Combination therapy provides substantially better response rates than monotherapy. Safety and efficacy have not been demonstrated for treatment longer than 48 weeks. Safety and efficacy have not been established in liver or other organ transplant recipients.</p> <p>Chronic hepatitis B</p> <p>Treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B in adults with compensated liver disease and evidence of viral replication and liver inflammation</p>
peginterferon alfa-2b (PEGIntron®, PEGIntron®, Redipen®) ³	Merck Sharp & Dohme	<p>Chronic hepatitis C</p> <ul style="list-style-type: none"> ▪ 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 (\geq18 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 <p>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.</p>

FDA-Approved Indications (continued)

Drug	Mfr	FDA-Approved Indications
Ribavirin		
ribavirin (Copegus™) ⁴	generic	<p>Chronic hepatitis C</p> <ul style="list-style-type: none"> 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 class A) Includes adult patients with clinically stable HIV disease and CD4 count > 100 cells/mm² <p>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.</p>
ribavirin (Rebetol®) ⁵	generic Merck Sharp & Dohme	<p>Chronic hepatitis C</p> <ul style="list-style-type: none"> In combination with interferon alfa-2b (pegylated [PEG-Intron] or non pegylated [Intron-A®]) in patients (≥ 3 years of age) with compensated liver disease <p>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 one year.</p>
ribavirin (Ribasphere™, Ribasphere Ribapak) ^{6,7,8}	generic	<p>Chronic hepatitis C</p> <p>Capsules</p> <ul style="list-style-type: none"> In combination with interferon alfa 2b (pegylated and non pegylated) in patients ≥3 years of age with compensated liver disease <p>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 one year.</p> <p>Tablets</p> <ul style="list-style-type: none"> 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 class A) and patients with HIV disease that is clinically stable and CD4 count > 100 cells/mm². <p>Safety and efficacy data are not available for treatment longer than 48 weeks. The safety and efficacy of ribavirin and peginterferon alfa-2a therapy has 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</p>

FDA-Approved Indications (continued)

Drug	Mfr	FDA-Approved Indications
Ribavirin		
ribavirin (Moderiba™) ⁹	Abbvie	<p>Chronic hepatitis C</p> <ul style="list-style-type: none"> ▪ 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 class A) and patients with HIV disease that is clinically stable and CD4 count > 100 cells/mm² <p>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.</p>
Oral Protease Inhibitors		
boceprevir (Victrelis™) ¹⁰	Merck Sharp & Dohme	<p>Chronic hepatitis C genotype 1 infection</p> <ul style="list-style-type: none"> ▪ In combination with peginterferon alfa and ribavirin, in adult patients (≥18 years of age) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy including prior null responders, partial responders and relapsers. ▪ The efficacy of boceprevir has not been studied in patients who have previously failed therapy with a treatment regimen that includes boceprevir or other HCV NS3/4A protease inhibitors. ▪ Boceprevir should only be used in combination with peginterferon and ribavirin; monotherapy should not be considered.
simeprevir (Olysio™) ¹¹	Janssen	<p>Chronic hepatitis C genotype 1 infection</p> <ul style="list-style-type: none"> ▪ In combination with peginterferon alfa and ribavirin in patients with compensated liver disease (including cirrhosis) or in combination with sofosbuvir ▪ Simeprevir monotherapy is not recommended ▪ Treatment regimen and duration are dependent on presence of cirrhosis ▪ 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 ▪ Efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that included simeprevir (Olysio) or other HCV protease inhibitors

FDA-Approved Indications (continued)

Drug	Mfr	FDA-Approved Indications
Oral Protease Inhibitors (continued)		
telaprevir (Incivek™) ¹²	Vertex	<p>Chronic hepatitis C genotype 1 infection</p> <ul style="list-style-type: none"> ▪ In combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have been previously treated with interferon-based treatments, including prior null responders, partial responders, and relapsers. ▪ Telaprevir must only be used in combination with peginterferon alfa and ribavirin; monotherapy should not be considered. <p>A high proportion of previous null responders (especially those with cirrhosis) did not achieve Sustained Virologic Response (SVR) and had telaprevir resistance-associated substitutions emerge on treatment. Efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes telaprevir or other HCV NS3/4A protease inhibitors.</p>
Oral NS5B Polymerase Inhibitors		
sofosbuvir (Sovaldi™) ^{13,14}	Gilead	<p>Chronic hepatitis C genotype 1,2,3, or 4</p> <ul style="list-style-type: none"> ▪ In combination with ribavirin alone or peginterferon and ribavirin ▪ Patients in whom efficacy was demonstrated included patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection ▪ Monotherapy with sofosbuvir is not recommended ▪ Treatment regimen and duration are dependent on both viral genotype and patient population ▪ Treatment response varies based on baseline host and viral factors
Oral Combination Products		
ledipasvir/sofosbuvir (Harvoni®) ¹⁵	Gilead	<p>Chronic hepatitis C genotype 1</p> <ul style="list-style-type: none"> ▪ Co-formulated fixed dose tablet of ledipasvir (an NS5A inhibitor) and sofosbuvir (an NS5B Inhibitor) ▪ Treatment duration is dependent on previous treatment experience, presence of cirrhosis, and baseline viral load ▪ Treatment response varies based on baseline host and viral factors
ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak®) ¹⁶	Abbvie	<p>Chronic hepatitis C genotype 1</p> <ul style="list-style-type: none"> ▪ Viekira Pak includes 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) ▪ In combination with ribavirin unless genotype 1b without cirrhosis ▪ Treatment regimen and duration are dependent on both viral genotype subtype and presence of cirrhosis

Vertex Pharmaceuticals announced plans to discontinue sales and distribution of telaprevir (Incivek) in the United States as of October 16, 2014. The manufacturer cited decreased demand and the presence of alternative therapies as the reason for discontinuation.

Merck has announced plans to voluntarily discontinue the manufacture and distribution of boceprevir (Victrelis) in the United States by December 2015. This was a business decision made by Merck and is not based on safety or efficacy findings with the product.

Kadmon Pharmaceuticals has discontinued the manufacturing of interferon alfacon-1 (Infergen) Injection as of March 31, 2014.

OVERVIEW

Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States (U.S.). In about 15 to 25 percent 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 percent of patients, the HCV persists for decades.¹⁷ Approximately 3.2 million people in the U.S. are chronically infected, although it is estimated that nearly 75 percent of these people may be unaware of their infection due to the insidious progression of the disease.¹⁸ HCV accounts for 40 percent 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 percent. Of those who develop cirrhosis, approximately 30 percent will develop end-stage liver disease over the next 10 years and one to two percent 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 percent 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 percent 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 1945-1965 account for 75 percent of all HCV infections. In August 2012, the CDC issued updated guidelines for HCV testing recommending all persons born from 1945-1965 (baby boomers) receive a one-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.

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 six 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 percent of U.S. infections; among African Americans, the frequency of genotype 1 is even higher at an estimated 90 percent.²⁹ In the U.S., genotype 1a and 1b represent about 75 percent and 25 percent of genotype 1 cases, respectively. Genotypes 2 and 3 account for the majority of the other approximate 25 to 30 percent of 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 percent. With the addition of ribavirin, dual therapy of peginterferon + ribavirin (PEG/RBV) therapy achieved SVR rates of 40 to 50 percent 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 percent were reported.^{33,34} In 2013, simeprevir (Olysio) and sofosbuvir (Sovaldi) were approved. Simeprevir is a second-generation protease inhibitor (classified along with telaprevir and boceprevir as an NS3/4A inhibitor). Simeprevir is approved for use in combination with sofosbuvir having an approximate SVR rate greater than 90 percent or for triple combination therapy with peginterferon and ribavirin associated with an approximate 80 percent 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, therefore, more favorable. Beginning with sofosbuvir, and continuing with subsequently approved treatments, SVR rates as high as 90 percent 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 approval. 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 a co-formulated formulation, it does represent another all-oral treatment option. The combination ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak), is the most recent treatment approved in December 2014. 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 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 include 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 ten to 15 percent of HCV infected patients. With consideration to resource limitations, the initiation of therapy should be prioritized 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. The patient population who would experience the most benefit from receiving treatment (at highest risk) are characterized as having advanced fibrosis (Metavir F3), compensated cirrhosis (Metavir F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C. Another group of patients, whose treatment would have a high impact on reducing further HCV transmission, are men with high-risk sexual practices (men who have sex with men), active injection drug users, incarcerated persons, and persons on long-term hemodialysis.

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) for each genotype. 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 often 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

Genotype 1^{38,39}

Treatment Experience	Treatment	Duration	Rating
Genotype 1a – Recommended Treatments			
Treatment Naïve	Patients without cirrhosis		
	▪ ledipasvir + sofosbuvir	8/12 weeks*	Class I, Level A
	▪ paritaprevir/ritonavir/ombitasvir + dasabuvir + weight-based ribavirin	12 weeks	Class I, Level A
	▪ sofosbuvir + simeprevir ± weight-based ribavirin	12 weeks	Class IIa, Level B
	Patients with cirrhosis		
	▪ ledipasvir + sofosbuvir	12 weeks	Class I, Level A
▪ paritaprevir/ritonavir/ombitasvir + dasabuvir + weight-based ribavirin	24 weeks	Class I, Level A	
▪ sofosbuvir + simeprevir ± weight-based ribavirin	24 weeks	Class IIa, Level B	
Genotype 1b – Recommended Treatments			
Treatment Naïve	Patients without cirrhosis		
	▪ ledipasvir + sofosbuvir	8/12 weeks*	Class I, Level A
	▪ paritaprevir/ritonavir/ombitasvir + dasabuvir	12 weeks	Class I, Level A
	▪ sofosbuvir + simeprevir	12 weeks	Class IIa, Level B
	Patients with cirrhosis		
	▪ ledipasvir + sofosbuvir	12 weeks	Class I, Level A
▪ paritaprevir/ritonavir/ombitasvir + dasabuvir + weight-based ribavirin	12 weeks	Class I, Level A	
▪ sofosbuvir + simeprevir	24 weeks	Class IIa, Level B	
Genotype 1 (regardless of subtype) – Recommended Treatments			
Treatment Experienced (previous failure of PEG/RBV)	Patients without cirrhosis		
	▪ ledipasvir + sofosbuvir	12 weeks	Class I, Level A
	▪ paritaprevir/ritonavir/ombitasvir + dasabuvir + weight-based ribavirin	12 weeks	Class I, Level A
	▪ sofosbuvir + simeprevir ± weight-based ribavirin	12 weeks	Class IIa, Level B
	Patients with compensated cirrhosis		
	▪ ledipasvir + sofosbuvir	24 weeks	Class I, Level A
▪ ledipasvir + sofosbuvir + weight-based ribavirin	12 weeks	Class I, Level B	
▪ paritaprevir/ritonavir/ombitasvir + dasabuvir + weight-based ribavirin	24 weeks	Class I, Level A	
▪ sofosbuvir + simeprevir ± weight-based ribavirin	24 weeks	Class IIa, Level B	
Treatment Experienced (previous failure of PEG/RBV + an HCV protease inhibitor)	Patients without cirrhosis		
	▪ ledipasvir + sofosbuvir	12 weeks	Class I, Level A
	Patients with compensated cirrhosis		
▪ ledipasvir + sofosbuvir	24 weeks	Class I, Level A	
▪ ledipasvir + sofosbuvir + weight-based ribavirin	12 weeks	Class IIa, Level B	
Treatment Experienced (previous failure of sofosbuvir containing regimen)	Patients without advanced fibrosis		
	▪ Based on the limited data available for effective therapy, patients without an urgent need for HCV treatment should defer antiviral therapy pending additional data or consider treatment within clinical trial settings		
Patients with advanced fibrosis			
▪ ledipasvir + sofosbuvir ± weight-based ribavirin	24 weeks		

Genotype 1 (regardless of subtype) – <u>NOT</u> Recommended Treatments			
Treatment Naïve	▪ sofosbuvir + weight based ribavirin	24 weeks	Class IIb, Level A
	▪ peginterferon + ribavirin ± sofosbuvir/simeprevir/telaprevir/boceprevir	12-48 weeks	Class IIb, Level A
	▪ monotherapy with peginterferon, ribavirin, or a direct acting antiviral	--	Class III, Level A
Treatment Experienced (previous failure of PEG/RBV + an HCV protease inhibitor)	▪ Any regimen containing PEG-IFN, including:	--	Class IIb Level A
	– simeprevir + peginterferon + ribavirin		
	– sofosbuvir + peginterferon + ribavirin		
	– telaprevir or boceprevir + peginterferon + ribavirin		
	– peginterferon + ribavirin		
	▪ Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral	--	Class III, Level A
▪ Any interferon-free regimen containing an HCV protease inhibitor	--	Class IIb, Level A	
	– simeprevir		
	– paritaprevir		

*Treatment naïve patients without cirrhosis and a baseline HCV RNA less than 6 million IU/mL can be considered for 8 weeks of treatment.

Genotype 2 ^{40,41}

Treatment Experience	Treatment	Duration	Rating
Genotype 2 – Recommended Treatments			
Treatment Naïve	Patients without cirrhosis		
	▪ sofosbuvir + weight-based ribavirin	12 weeks	Class I, Level A
	Patients with compensated cirrhosis		
	▪ sofosbuvir + weight-based ribavirin	16 weeks	Class IIb, Level C
Treatment Experienced (previous failure of PEG/RBV)	▪ sofosbuvir + weight-based ribavirin	12-16 weeks	Class I, Level A
Genotype 2 – Alternative Treatments			
Treatment Experienced (previous failure of PEG/RBV)	▪ sofosbuvir + weight-based ribavirin + peginterferon	12 weeks	Class IIa Level B
Genotype 2 – <u>NOT</u> Recommended Treatments			
Treatment Naïve	▪ peginterferon + ribavirin	24 weeks	Class IIb, Level A
	▪ monotherapy with peginterferon, ribavirin, or a direct acting antiviral	--	Class III, Level A
	▪ telaprevir, boceprevir, or ledipasvir containing regimens	--	Class III, Level A
Treatment Experienced (previous failure of PEG/RBV)	▪ PEG-IFN and RBV with or without telaprevir or boceprevir	--	Class IIb, Level A
	▪ ledipasvir + sofosbuvir	--	Class III, Level A
	▪ monotherapy with PEG-IFN, RBV, or a direct-acting antiviral	--	Class III, Level A

There is no alternative regimen listed for treatment naïve genotype 2 patients.

Genotype 3 ^{42,43}

Treatment Experience	Treatment	Duration	Rating
Genotype 3 – Recommended Treatments			
Treatment Naïve	▪ sofosbuvir + weight-based ribavirin	24 weeks	Class I, Level B
Treatment Experienced (previous failure of PEG/RBV)	▪ sofosbuvir + weight-based ribavirin	24 weeks	Class I, Level B
Genotype 3 – Alternative Treatments			
Treatment Naïve	▪ sofosbuvir + weight-based ribavirin + peginterferon	12 weeks	Class IIa, Level A
Treatment Experienced (previous failure of PEG/RBV)	▪ sofosbuvir + weight-based ribavirin + peginterferon	12 weeks	Class IIa, Level B
Genotype 3 – <u>NOT</u> Recommended Treatments			
Treatment Naïve	▪ peginterferon + ribavirin ▪ monotherapy with peginterferon, ribavirin, or a direct acting antiviral ▪ telaprevir, boceprevir, or simeprevir based regimens	24-48 weeks -- --	Class IIb, Level A Class III, Level A Class III, Level A
Treatment Experienced (previous failure of PEG/RBV)	▪ peginterferon + ribavirin ▪ monotherapy with peginterferon, ribavirin, or a direct-acting antiviral ▪ telaprevir, boceprevir, or simeprevir-based regimens	24-48 weeks -- --	Class IIb, Level A Class III, Level A Class III, Level A

Genotype 4 ^{44,45}

Treatment Experience	Treatment	Duration	Rating
Genotype 4 – Recommended Treatments			
Treatment Naïve	▪ ledipasvir + sofosbuvir	12 weeks	Class IIb, Level B
	▪ paritaprevir/ritonavir/ombitasvir + weight-based ribavirin	12 weeks	Class I, Level B
	▪ sofosbuvir + weight-based ribavirin	24 weeks	Class IIa, Level B
Treatment Experienced (previous failure of PEG/RBV)	▪ ledipasvir + sofosbuvir	12 weeks	Class IIa, Level B
	▪ paritaprevir/ritonavir/ombitasvir + weight-based ribavirin	12 weeks	Class IIa, Level B
	▪ sofosbuvir + weight-based ribavirin + peginterferon	12 weeks	Class IIa, Level B
	▪ sofosbuvir + weight-based ribavirin	24 weeks	Class IIa, Level B
Genotype 4 – Alternative Treatments			
Treatment Naïve	▪ sofosbuvir + weight-based ribavirin + peginterferon	12 weeks	Class II, Level B
	▪ sofosbuvir + simeprevir ± weight-based ribavirin	12 weeks	Class IIb, Level B
Genotype 4 – NOT Recommended Treatments			
Treatment Naïve	▪ peginterferon + ribavirin ± simeprevir	24-48 weeks	Class IIb, Level A
	▪ monotherapy with peginterferon, ribavirin, or a direct acting antiviral	--	Class III, Level A
	▪ telaprevir or boceprevir based regimens	--	Class III, Level A
Treatment Experienced (previous failure of PEG/RBV)	▪ peginterferon + ribavirin ± telaprevir or boceprevir	--	Class IIb, Level A
	▪ monotherapy with peginterferon, ribavirin, or a direct acting antiviral	--	Class III, Level A

Genotype 5 and 6^{46,47}

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

Treatment Experience	Treatment	Duration	Rating
Genotype 5 – Recommended Treatments			
Treatment Naïve	▪ sofosbuvir + weight-based ribavirin + peginterferon	12 weeks	Class IIa, Level B
Treatment Experienced	▪ sofosbuvir + weight-based ribavirin + peginterferon	12 weeks	Class IIa, Level B
Genotype 5 – Alternative Treatments			
Treatment Naïve	▪ peginterferon + weight based ribavirin	48 weeks	Class IIa, Level A
Treatment Experienced	▪ peginterferon + weight based ribavirin	48 weeks	Class IIb, Level A
Genotype 6 – Recommended Treatments			
Treatment Naïve	▪ ledipasvir + sofosbuvir	12 weeks	Class IIa, Level B
Treatment Experienced	▪ ledipasvir + sofosbuvir	12 weeks	Class IIa, Level B
Genotype 6 – Alternative Treatments			
Treatment Naïve	▪ sofosbuvir + weight-based ribavirin + peginterferon	12 weeks	Class IIa, Level B
Treatment Experienced	▪ sofosbuvir + weight-based ribavirin + peginterferon	12 weeks	Class IIa, Level B
Genotype 5 or 6 – <u>NOT</u> Recommended Treatments			
Treatment Naïve	▪ monotherapy with peginterferon, ribavirin, or a direct acting antiviral ▪ telaprevir or boceprevir based regimens	-- --	Class III, Level A Class III, Level A
Treatment Experienced	▪ monotherapy with peginterferon, ribavirin, or a direct acting antiviral ▪ telaprevir or boceprevir based regimens	-- --	Class III, 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

PHARMACOLOGY

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.⁴⁸ Because of their long half-lives, peginterferons can be administered subcutaneously (SC) once weekly. Interferon alfacon-1 (Infergen) is a non-naturally occurring, synthetic type-I interferon alfa.⁴⁹

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 is a nucleoside analog with antiviral activity.⁵⁰ 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.^{51,52} The mechanism of inhibition of HCV RNA by combination therapy with interferon alfa and ribavirin has not been established.⁵³

DAA are newer medications approved for the treatment of HCV. One group of DAAs are classified as protease inhibitors and consist of boceprevir (Victrelis), telaprevir (Incivek), simeprevir (Olysio), and paritaprevir (available as part of Viekira Pak). Boceprevir, paritaprevir, simeprevir, and telaprevir inhibit hepatitis C NS3/4A protease, which is essential for replication of the virus.

Sofosbuvir (Sovaldi) and dasabuvir (available as part of Viekira Pak) 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.⁵⁴ Dasabuvir targets the palm domain of the NS5B polymerase, and is referred to as a non-nucleoside NS5B-palm polymerase inhibitor.⁵⁵

Another group of DAAs are the NS5A inhibitors and consist of ledipasvir (co-formulated with sofosbuvir and available as Harvoni) and ombitasvir (available as part of Viekira Pak).^{56,57} These agents inhibit the HCV NS5A, which is essential for viral RNA replication and virion assembly.

PHARMACOKINETICS

The half-life of interferon alfa is approximately five to eight hours. Dosing these agents three times weekly results in undetectable blood levels of interferon during the remaining four 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.^{58,59} The shorter half-life of peginterferon alfa-2b (PEGIntron) results in undetectable levels at day seven while peginterferon alfa-2a (PEGASYS) accumulates over time with multiple dosing. The pharmacokinetic profile of interferon alfacon-1 (Infergen) has not been completed in patients with chronic hepatitis C.⁶⁰

In patients with end-stage renal disease undergoing hemodialysis, there is a 25 to 45 percent reduction in clearance of peginterferon alfa-2a (PEGASYS).⁶¹ There is a 44 percent reduction in peginterferon alfa-2b (PEGIntron) clearance in patients with creatinine clearance (CLCR) less than 30 mL/min.⁶² Dose reductions for both peginterferons are necessary for patients with moderate renal impairment.

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.

Bioavailability of boceprevir (Victrelis) has not been studied; however, boceprevir may be taken without regard to meals.⁶³ Boceprevir is administered as an approximately equal mixture of two diastereomers, SCH534128 and SCH534129, which rapidly interconvert in plasma. The predominant diastereomer, SCH534128, is pharmacologically active and the other diastereomer is inactive. Boceprevir primarily undergoes metabolism through the aldo-ketoreductase-mediated pathway to ketone-reduced metabolites that are inactive against HCV.

Telaprevir (Incivek) absorption is significantly reduced when administered during a fast or with a low-fat meal. Telaprevir should always be taken with food (not low fat). Telaprevir is extensively metabolized in the liver, involving hydrolysis, oxidation, and reduction. Multiple metabolites were detected in feces, plasma, and urine. Estimated half-life of telaprevir is nine to 11 hours.

Administration of simeprevir (Olysio) with food to healthy subjects increased the relative bioavailability (AUC) by 61 percent and 69 percent after a high fat, high caloric (928 kcal), and normal-caloric (533 kcal) breakfast, respectively, and delayed the absorption by one hour and 1.5 hours, respectively.⁶⁴ Simeprevir is extensively bound to plasma proteins (greater than 99.9 percent), 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.

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 percent of drug related material systemic exposure, while the parent sofosbuvir accounts for approximately four percent of drug related material.⁶⁵ Following oral administration of sofosbuvir under fasting conditions, peak plasma concentrations were observed at 0.5 to two 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 reaches its mean peak concentration approximately four to 4.5 hours after oral administration.⁶⁶ 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 reaches its mean peak concentration approximately four to five hours after oral administration.⁶⁷ The absolute bioavailability of dasabuvir is approximately 70 percent 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. 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.

CONTRAINDICATIONS/WARNINGS

Interferons^{68,69,70}

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 score > 6 [class B and C]) in cirrhotic chronic hepatitis C patients before treatment. Peginterferon alfa-2a (PEGASYS) is contraindicated in hepatic decompensation (Child-Pugh score ≥ 6) in cirrhotic chronic hepatitis C patients co-infected with HIV before treatment.

Peginterferon alfa-2b (PEGIntron) is contraindicated in hepatic decompensation (Child-Pugh score > 6 [class 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.

Contraindications for interferon alfacon-1 (Infergen) include known hypersensitivity to alpha interferons, autoimmune hepatitis, and decompensated hepatic disease (Child-Pugh score ≥ 6 [Class B and C]).

The combination of peginterferon or interferon alfacon-1 plus ribavirin are contraindicated in women who are pregnant or may become pregnant, men whose female partners are pregnant, patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia), and in patients with creatinine clearance < 50 mL/minute.

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.

Warnings

All of the alpha interferons indicated for HCV, including peginterferons and interferon alfacon-1 (Infergen), have the following black box 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 or interferon alfacon-1 (Infergen). 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. 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.

Interferon 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 X 10⁹/L) or platelet counts (<25 X 10⁹/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.

Interferon 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.

Interferon 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 percent of 254 patients being treated for chronic hepatitis C with interferon alfa plus ribavirin combination therapy.⁷¹ 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 an interferon 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 interferon 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 interferon 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.

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

Ribavirin^{72,73,74,75,76}

Contraindications

Ribavirin is contraindicated in patients with hemoglobinopathies (e.g., thalassemia major, sickle cell anemia).⁷⁷ 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 two effective forms of contraception during therapy and for six months after treatment has stopped.

Monthly pregnancy testing should be performed during and for six months after therapy has been discontinued. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen.

Ribavirin is contraindicated in patients with autoimmune hepatitis, hepatic decompensation (Child-Pugh score >6; class B or C) in cirrhotic patients with chronic hepatitis C before or during therapy, and hepatic decompensation (Child-Pugh score \geq 6) 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 percent of patients treated with interferon alfa plus ribavirin in clinical trials and usually occurred within one to two weeks of initiation of ribavirin therapy. Cardiac and pulmonary events have occurred in approximately 10 percent 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.

Oral Protease Inhibitors – boceprevir (Victrelis), simeprevir (Olysio) and telaprevir (Incivek)^{78,79,80}

Contraindications

All contraindications to peginterferon alfa and ribavirin also apply when boceprevir (Victrelis), simeprevir (Olysio), or telaprevir (Incivek) are administered with peginterferon alfa and ribavirin. Due to the ribavirin in the triple combination therapy, boceprevir, simeprevir, and telaprevir plus peginterferon/ribavirin are contraindicated in pregnant women and in men whose female partners are pregnant. Because ribavirin may cause birth defects and fetal death, avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to therapy, use two or more forms of contraception, and have monthly pregnancy tests.

Patients with a hypersensitivity reaction to boceprevir are contraindicated.

The triple combination with boceprevir (Victrelis) or telaprevir (Incivek) is contraindicated in patients who have concurrent drug therapy with drugs that are highly dependent on CYP 3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life threatening events. The following drugs are contraindicated with boceprevir (Victrelis) and telaprevir (Incivek): alfuzosin (increased alfuzosin levels resulting in hypotension or cardiac arrhythmias), dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential for acute ergot toxicity characterized by peripheral vasospasm or ischemia), cisapride and pimozide (potential for cardiac arrhythmias), simvastatin and lovastatin (potential for myopathy, including rhabdomyolysis), sildenafil and tadalafil when used for the treatment of pulmonary arterial hypertension (potential for PDE5 inhibitor-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope), and orally-administered triazolam and midazolam (prolonged or increased sedation or respiratory depression). Boceprevir (Victrelis) is also contraindicated with drospirenone, carbamazepine, phenobarbital, phenytoin, **doxazosin, silodosin, and tamsulosin**. Telaprevir (Incivek) is also contraindicated with atorvastatin.

Potent CYP 3A4/5 inducers may significantly reduce boceprevir (Victrelis) plasma concentrations. The following drugs are contraindicated with concurrent administration of boceprevir due to the potential for reduced efficacy of boceprevir: carbamazepine, rifampin, phenytoin, phenobarbital, and St. John's wort.

Co-administration with potent CYP 3A4 inducers may significantly reduce telaprevir (Incivek) plasma concentrations and lead to loss of efficacy. The following drugs are contraindicated with concurrent administration of telaprevir due to the potential for reduced efficacy of telaprevir: rifampin, carbamazepine, phenobarbital, phenytoin, and St. John's wort. Telaprevir is a strong CYP 3A inhibitor and is contraindicated when combined with drugs that depend on CYP 3A for clearance when elevated levels of that drug are associated with serious adverse events.

Neuroleptic drugs, such as pimozide, may result in serious and/or life-threatening adverse reactions, such as cardiac arrhythmias, when administered with telaprevir.

Warnings

The addition of boceprevir (Victrelis) or telaprevir (Incivek) to peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations. Hemoglobin levels should be checked before beginning telaprevir and at weeks 2, 4, 8, and 12 weeks of therapy. If ribavirin dose reductions are insufficient to manage anemia, telaprevir may need to be discontinued. Chemistry evaluations (including electrolytes, serum creatinine, uric acid, hepatic enzymes, bilirubin, and TSH) are recommended as frequently as hematology evaluations or as clinically appropriate. Boceprevir in triple combination therapy is associated with additional worsening of neutropenia compared with peginterferon alfa and ribavirin alone.

Telaprevir (Incivek) prescribing information contains a boxed warning regarding fatal and non-fatal serious skin reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson syndrome (SJS), and Toxic Epidermal Necrolysis (TEN). Fatal reactions have been reported in patients with serious skin reactions who continued therapy after a progressive rash was identified. Therapy with telaprevir, peginterferon, and ribavirin should be discontinued immediately for serious reactions, including rash with systemic symptoms or a progressive severe rash, and patients should be promptly referred for urgent medical care. Other drugs known to be associated with severe rash should also be discontinued. During the clinical trial program, serious skin reactions (including DRESS and SJS) were reported in less than one percent of patients receiving telaprevir. Patients in trials were hospitalized and all subjects recovered.

Rash develops in a significant proportion of telaprevir (Incivek)-treated patients. The rash observed with telaprevir is typically a maculopapular and papular lichenoid rash. It is similar to that reported with pegylated interferon and ribavirin. Patients with mild to moderate rash should be followed for progression of rash or development of systemic symptoms. If the rash becomes severe or if systemic symptoms develop, telaprevir should be discontinued. If the rash does not improve within seven days, sequential or simultaneous interruption or discontinuation of ribavirin and/or peginterferon alfa should be considered. If telaprevir is discontinued due to rash, it must not be re-started.

Boceprevir (Victrelis), in combination with peginterferon alfa and ribavirin, has been associated with serious acute hypersensitivity reactions including urticaria and angioedema. Boceprevir should be discontinued in patients exhibiting serious hypersensitivity reactions and medical therapy immediately provided.

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 four 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 four 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.

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.

Oral NS5B Polymerase Inhibitors – sofosbuvir (Sovaldi) ⁸¹

Contraindications

When used in combination with peginterferon and ribavirin or ribavirin alone, all contraindications to peginterferon and/or ribavirin also apply to sofosbuvir (Sovaldi) combination therapy.

Due to the risks for birth defects and fetal death associated with ribavirin, combination therapy with sofosbuvir plus ribavirin or sofosbuvir plus peginterferon and ribavirin is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant. Women of childbearing potential and their male partners must use two forms of effective contraception during treatment and for at least six months after treatment has ended. Routine monthly pregnancy tests should be performed during this time.

Warnings

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. 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.

Ledipasvir/sofosbuvir (Harvoni)⁸²

Contraindications

There are no contraindications to treatment with ledipasvir/sofosbuvir.

Warnings

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.

Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir (Viekira Pak)⁸³

Contraindications

If ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak) is administered with ribavirin, the contraindications to ribavirin apply to the combination regimen. Ribavirin is contraindicated for use during pregnancy, in females who may become pregnant, and in men whose female partners are pregnant. Ribavirin is also contraindicated in patients with hemoglobinopathies (e.g., thalassemia major or sickle cell anemia), autoimmune hepatitis or patients with hepatic decompensation (Child-Pugh score greater than six, class B and C). Ribavirin is also contraindicated for use in combination with didanosine.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak) is contraindicated in patients with severe hepatic impairment.

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

Warnings

There is an increased risk of ALT elevations in patients taking ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak) with or without ribavirin. Elevations of ALT to greater than five times the upper limit of normal (ULN) occurred in approximately one percent of all subjects during clinical trials. ALT elevations typically occurred during the first four weeks of treatment and declined within two to eight weeks of onset with continued dosing of Viekira Pak 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 four weeks of starting treatment and as clinically indicated thereafter. Consideration should be given to discontinuing ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak) if ALT levels remain persistently greater than ten times the ULN. Ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak) 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) 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) should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

Risk Evaluation and Mitigation Strategy (REMS)

The FDA no longer requires a medication guide be given to the patient with each prescription for peginterferon alfa-2a (PEGASYS or Peg-Intron) or ribavirin (Rebetol or Copegus).^{84,85,86,87} Both boceprevir (Victrelis) and telaprevir (Incivek) require a medication guide be given to the patient with each prescription.^{88,89}

DRUG INTERACTIONS^{90,91,92,93,94,95}

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 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 three to seven weeks after the concomitant administration with peginterferon and ribavirin with

azathioprine. In the eight reported cases, myelosuppression was reversible over four to six weeks upon withdrawal of all three agents and did not recur upon reintroduction of either treatment alone.

Telaprevir (Incivek) is a strong inhibitor of CYP3A4. Co-administration of telaprevir with drugs that are metabolized by CYP3A4 may result in increased plasma concentrations with increased pharmacologic effects or adverse reactions. Telaprevir is primarily metabolized by CYP3A4. Co-administration of telaprevir with drugs that inhibit CYP3A may increase telaprevir plasma concentrations; drugs that induce CYP3A4 may reduce telaprevir concentrations and its efficacy. The potential for drug-drug interactions must be considered prior to and during therapy. Telaprevir also inhibits P-glycoprotein (P-gp), OATP1B1 and OATP2B1 transporters. Administration of telaprevir with drugs that are substrates for these transporters may result in increased concentrations of those drugs and dosing should be adjusted as indicated.

Boceprevir (Victrelis) is a strong inhibitor of CYP3A4/5 and is partially metabolized by CYP3A4/5.

Co-administration of simeprevir (Olysio) with moderate or strong inducers (e.g., carbamazepine, phenobarbital, phenytoin, etc.) or inhibitors (e.g., ritonavir, ketoconazole, clarithromycin, etc.) 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.

Boceprevir (Victrelis) and telaprevir (Incivek), have extensive drug interactions with significant need for increased monitoring and/or dosage adjustments. Both of these protease inhibitors may have drug interactions with the following drug classes and drugs and may require increased monitoring or dosage adjustment (list is not all inclusive): anti-arrhythmics, digoxin, azole antifungals, colchicine, systemic or inhaled corticosteroids, bosentan, efavirenz, methadone, ethinyl estradiol, alprazolam, and IV midazolam.

For telaprevir (Incivek), additional drug classes and drugs impacted by concurrent administration include (list is not all-inclusive): atorvastatin, warfarin, anticonvulsants, calcium channel blockers, macrolides, protease inhibitors indicated for HIV, and tenofovir. Drug classes and drugs that may interact with boceprevir (Victrelis) include the following (list is not all-inclusive): clarithromycin, ritonavir, atorvastatin, immunosuppressants, salmeterol, buprenorphine, and drospirenone. See prescribing information for specific recommendations and details for boceprevir and telaprevir.

Administration of boceprevir (Victrelis) with HIV protease inhibitors (atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir, and ritonavir) is not recommended. When boceprevir is co-administered with cyclosporine or tacrolimus, dose adjustments may be necessary guided by blood concentrations of cyclosporine or tacrolimus, renal function monitoring, and side effect assessment. Tacrolimus requires significant dose reduction and prolongation of the dosing interval for tacrolimus. Doses of escitalopram may need to be adjusted when administered with boceprevir. Levels of atorvastatin and pravastatin were both increased when administered with boceprevir. Atorvastatin doses should not exceed a total of 40 mg/day when administered concurrently. Close monitoring may be necessary.

Drug interactions between telaprevir (Incivek) and raltegravir or buprenorphine were evaluated in clinical trials but no dose adjustment is needed for either drug.

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 (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 co-administration is not recommended.

Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease the concentration of ledipasvir. Antacids, H₂-receptor antagonists (e.g., famotidine), 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.

Coadministration 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 coadministration 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 coadministration is not recommended.

Coadministration of ledipasvir/sofosbuvir with rosuvastatin may significantly increase the concentration of rosuvastatin leading to an increased risk of myopathy, including rhabdomyolysis. Coadministration with rosuvastatin is not recommended.

Co-administration of ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak) with strong inhibitors of CYP3A may increase paritaprevir and ritonavir concentrations. Co-administration of Viekira Pak 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.

Co-administration of Viekira Pak 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.

Concomitant therapy with Viekira Pak could increase concentrations of the following interacting medications: antiarrhythmics (amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine), antifungals (ketoconazole), calcium channel blockers (amlodipine), corticosteroids (fluticasone), diuretics (furosemide), HMG CoA Reductase Inhibitors (rosuvastatin, pravastatin), immunosuppressants (cyclosporine, tacrolimus), narcotic analgesics (buprenorphine), and sedatives/hypnotics (alprazolam).

Concomitant therapy with Viekira Pak could decrease the concentration omeprazole.

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

Adverse Effects

Drug	Depression	Fever	Injection Site Reaction	Anemia	Neutropenia	Withdrawal Rate
Monotherapy						
interferon alfacon-1 (Infergen) ⁹⁶ n=231	26	61	23	4	19	nr
peginterferon alfa-2a (PEGASYS) ⁹⁷ n=559	18	37	22	2	21	11
peginterferon alfa-2b (PEGIntron) ⁹⁸ n=297	29	22	47	0	6	10–14
Dual Combination Therapy						
interferon alfacon-1 (Infergen) ⁹⁹ n=486	25–27	13–17	12–15	27	24–34	21
peginterferon alfa-2a (PEGASYS) ¹⁰⁰ + ribavirin n=451	20	41	23	11	27	11
peginterferon alfa-2a (PEGASYS) ¹⁰¹ + ribavirin n=55	nr	nr	44	nr	nr	13
peginterferon alfa-2b (PEGIntron) ¹⁰² + ribavirin n=511 adults	31	46	75	12	26	10–14
peginterferon alfa-2b (PEGIntron) ¹⁰³ + ribavirin n=107 pediatric patients	1	80	29	11	33	2
ribavirin + sofosbuvir (Sovaldi) for 24 weeks ¹⁰⁴ n=250	nr	4	N/A	6	<1	<1

Adverse Effects (continued)

Drug	Rash	Dysgeusia	Fatigue	Anemia	Neutropenia	Withdrawal Rate
Triple Combination Therapy						
boceprevir (Victrelis) plus peginterferon alfa-2b/ribavirin n=1,225	17	35	58	50	25	13
peginterferon alfa-2b/ribavirin n=467	191	16	59	30	19	12
telaprevir (Incivek) plus peginterferon alfa/ribavirin n=1,797	56	10	56	36	15	14
peginterferon alfa/ribavirin n=493	34	3	50	17	5	nr
simeprevir (Olysio) plus peginterferon alfa/ribavirin ¹⁰⁵ 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 ¹⁰⁶ n=327	18	nr	59	21	17	2
peginterferon alfa/ribavirin for 24 weeks n=243	18	nr	55	12	12	11

Adverse Effects (continued)

Drug	Fatigue	Headache	Nausea	Diarrhea	Insomnia	Pruritus	Asthenia	Withdrawal Rate
All Oral Combination Therapy								
ledipasvir/sofosbuvir (Harvoni) for 8 weeks ¹⁰⁷ n=215	16	11	6	4	3	nr	nr	0
ledipasvir/sofosbuvir (Harvoni) for 12 weeks ¹⁰⁸ n=539	13	14	7	3	5	nr	nr	<1
ledipasvir/sofosbuvir (Harvoni) for 24 weeks ¹⁰⁹ n=326	18	17	9	7	6	nr	nr	1
ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak) + ribavirin for 12 weeks ¹¹⁰ 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) + ribavirin for 12 weeks ¹¹¹ in patients without cirrhosis n=401	nr	nr	16	nr	12	13	9	<1
ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak) for 12 weeks in patients without cirrhosis n=509	nr	nr	8	nr	5	7	4	<1
simeprevir + sofosbuvir ¹¹² n=167	25	21	21	nr	14	11	nr	2

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 three percent of subjects treated with combination peginterferon, ribavirin, and simeprevir (Olysio) in clinical trials included pruritus (22 percent versus 20 percent in placebo group), nausea, (22 percent versus 18 percent) myalgia (16 percent versus 13 percent), and dyspnea (12 percent versus eight percent). In the simeprevir treated groups, 27 percent experienced grade one hyperbilirubinemia compared to 15 percent of patients in the placebo arm. Grade two hyperbilirubinemia was seen in 18 percent of simeprevir treated patients versus nine percent of patients in the placebo arm.

The most common adverse events (≥ 20 percent) for sofosbuvir (Sovaldi) plus ribavirin combination therapy were fatigue and headache. The most common adverse events (≥ 20 percent) 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 one 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.

Treatment adherence enhances SVR in patients with genotype 1 HCV.¹¹³ Therefore, management of adverse effects to maintain patients on at least 80 percent of interferon or peginterferon alfa and ribavirin therapy for at least 80 percent of the duration of therapy will likely increase the chance for SVR.

Laboratory abnormalities occurring in less than five percent 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 three times the ULN.

The most common adverse events occurring in at least ten percent of patients treated with Viekira Pak and ribavirin who were co-infected with HCV/HIV included fatigue (48 percent), insomnia (19 percent), nausea (17 percent), headache (16 percent), pruritus (13 percent), cough (11 percent), irritability (10 percent), and ocular icterus (10 percent). Median declines in CD4+ T-cells of 47 cells/mm³ and 62 cells/mm³ 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 percent of the 34 post-liver transplant subjects treated with Viekira Pak and ribavirin were fatigue (50 percent), headache (44 percent), cough (32 percent), diarrhea (26 percent), insomnia (26 percent), asthenia (24 percent), nausea (24 percent), muscle spasms (21 percent), and rash (21 percent). Ten of the 34 subjects underwent a ribavirin dose modification due to a decrease in hemoglobin and one patient required an interruption of ribavirin.

Post-baseline elevations in bilirubin at least 2 x ULN were observed in 15 percent of patients across all Phase 3 studies receiving Viekira Pak with ribavirin compared to two percent of patients receiving Viekira Pak 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 percent of subjects experienced total bilirubin elevations greater than 2 x ULN. Approximately half of the HCV/HIV co-infected patients who developed a bilirubin elevation greater than 2 x ULN were also receiving atazanavir.

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

SPECIAL POPULATIONS

Pediatrics

An estimated 240,000 children in the U.S. in 2002 had antibodies to HCV.¹¹⁴ The seroprevalence is 0.2 percent for children ages six to 11 years and 0.4 percent for those 12 to 19 years of age.¹¹⁵ New HCV infections in children are primarily the result of perinatal transmission.¹¹⁶ The 2009 AASLD practice guidelines for the treatment of hepatitis C recommend that children ages two 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 two to 17 years: peginterferon alfa-2b (PEGIntron) 60 mcg/m² SC weekly with ribavirin 15 mg/kg daily for 48 weeks. The 2011 AASLD guidelines did not cover the treatment of pediatric patients other than to say that telaprevir (Incivek) and boceprevir (Victrelis) 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.¹¹⁷ **The updated AASLD/IDSA hepatitis C guidelines do not address HCV in pediatric patients.**

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 percent.¹¹⁸ In a small published trial, safety and efficacy of peginterferon alfa-2b (PEGIntron) plus ribavirin have been evaluated in 30 children (ages three to 16 years) with detectable HCV for a minimum of three years.¹¹⁹ 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 percent of patients (100 percent of genotype 3; 12/27 patients with genotypes 1 or 4). For EVR at week 12, 52 percent of patients were HCV RNA negative. Three patients discontinued therapy due to adverse effects. Dose reductions of peginterferon alfa-2b were required in 23 percent 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/1.73m² 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 percent in the peginterferon alfa plus ribavirin group versus 21 percent in the peginterferon alfa monotherapy group (p<0.001).¹²⁰ For those patients with genotype 1 HCV, SVR was obtained in 47 percent and 17 percent of the combination and monotherapy groups, respectively. Neutropenia or anemia leads to dose modification in about 30 percent of children. At the two-year follow-up visit, in the 82 percent of combination therapy and 86

percent of monotherapy patients available for analysis of durability of response, virologic response was 100 percent in both groups.

Another published study evaluated peginterferon alfa-2a (PEGASYS) in a trial with 14 children ages two to eight years with chronic hepatitis C.¹²¹ 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 percent 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.¹²² After about six months post-treatment, subjects had weight gain rebounds similar to that predicted by their average baseline weight. After about six 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 (< three percentile) was observed in 70 percent of patients while on treatment. Of the subjects experiencing severely inhibited growth, 20 percent had continued inhibited growth velocity (< third percentile) after six months of follow-up. Long-term follow-up data in pediatric subjects indicates that peginterferon combination therapy with ribavirin may induce a growth inhibition that results in reduced adult height in some patients.¹²³

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.¹²⁴ On follow-up at two years post-treatment, most patients had returned to their baseline normative growth curve percentiles, but 16 percent of patients remained 15 percentiles or more below their baseline weight curve and 11 percent 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.

Interferon alfacon-1 (Infergen) has not been shown to be safe and effective in children less than 18 years old.¹²⁵

Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4 versus one percent) during treatment with ribavirin and off-therapy follow-up.¹²⁶

Safety and effectiveness of boceprevir (Victrelis), **ledipasvir/sofosbuvir (Harvoni)**, **ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak)**, simeprevir (Olysio), telaprevir (Incivek), and sofosbuvir (Sovaldi) have not been established in pediatric patients.^{127,128,129,130,131,132}

Pregnancy^{133,134,135,136,137,138,139,140,141,142}

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.

Peginterferon alfa-2a (PEGASYS), peginterferon alfa-2b (PEGIntron), and interferon alfacon-1 (Infergen) are Pregnancy Category C.

Boceprevir (Victrelis), ledipasvir/sofosbuvir (Harvoni), sofosbuvir (Sovaldi), and telaprevir (Incivek) are Pregnancy Category B, while simeprevir (Olysio) is Pregnancy Category C.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak) is Pregnancy Category B. When administered with ribavirin, this combination 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 regimen should be considered that of the most restrictive individual drug used in the combination regimen.

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.^{143,144,145} The reasons for these differences are not known.¹⁴⁶

Patients of East Asian ancestry exhibit higher simeprevir (Olysio) exposures, which have been associated with increased frequency of adverse reactions, including rash and photosensitivity.¹⁴⁷ 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.

Co-infected HCV/HIV Patients

HIV infection is independently associated with advanced liver fibrosis and cirrhosis in patients with HCV co-infection. 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.¹⁴⁸

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

There are three 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.

Phase 3 trials of the protease inhibitors included evaluations of treatment-experienced patients with genotype 1 chronic HCV infection. For both boceprevir (Victrelis) and telaprevir (Incivek), studies showed that retreatment with triple therapy was superior to retreatment with peginterferon plus ribavirin in obtaining a SVR.^{149,150} Patients who had relapsed have higher response rates (SVR) on retreatment compared to those with a prior partial response. Null responders have the lowest

response rate; retreatment of null responders with the telaprevir (Incivek) containing triple therapy regimen produced SVR rates of 28 percent. Null responders re-treated with boceprevir (Victrelis) containing triple therapy for 44 weeks had a SVR rate of 38 percent (20 of 52) with a relapse rate of 14 percent (3/20).¹⁵¹

As noted in the Overview section, the AASLD/IDSA guidelines include recommendations for treating patients who relapsed after prior therapy.¹⁵²

Renal Impairment^{153,154,155,156}

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.¹⁵⁷

According to the prescribing information, the peginterferon alfa-2b (PEGIntron) dose should be reduced by 25 percent 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 percent. 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.

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 end stage renal disease 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 is no data available on dosage adjustments for renal failure in pediatric patients.¹⁵⁸

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.¹⁵⁹ The prescribing information for Rebetol states that ribavirin should not be used in patients with a CrCl < 50 mL/minute.¹⁶⁰

Interferon alfacon-1 plus ribavirin should not be administered to patients with creatinine clearance <50 mL/minute.

No dosage adjustment of telaprevir (Incivek) or simeprevir (Olysio) is required for patients with mild, moderate, or severe renal impairment. Neither of these agents has been studied in patients with end stage renal dysfunction or those on hemodialysis.

No dosage adjustment is required for boceprevir (Victrelis) with renal impairment.

No dosage adjustments are required for ledipasvir/sofosbuvir in patients with mild or moderate renal impairment. The safety and efficacy of ledipasvir/sofosbuvir has not been evaluated in patients with severe renal impairment (CrCl<30 mL/min/1.73m²) or end-stage renal disease (ESRD) requiring dialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD.

No dosage adjustments are required for ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak) in patients with mild, moderate or severe renal impairment. Viekira Pak has not been studied in patients on dialysis.

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

Hepatic Impairment^{161,162,163}

FDA approved labeling states no dosage adjustment of telaprevir (Incivek) or simeprevir (Olysio) is necessary for patients with mild hepatic impairment (Child-Pugh A, score 5-6).

No dosage adjustment of ledipasvir/sofosbuvir is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C). Safety and efficacy of ledipasvir/sofosbuvir have not been established in patients with decompensated cirrhosis.

No dosage adjustment of ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak) is required for patients with mild hepatic impairment (Child-Pugh Class A). Viekira Pak is not recommended in patients with moderate hepatic impairment (Child-Pugh Class B). Viekira Pak is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C).

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

No dose adjustment of boceprevir (Victrelis) is required for patients with mild, moderate, or severe hepatic impairment. However, safety and efficacy of boceprevir (Victrelis) have not been studied in patients with decompensated cirrhosis or in patients with an organ transplant.

Telaprevir (Incivek) is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh B or C, score ≥ 7) because there is little information on its pharmacokinetics, safety, or the appropriate dosage in this population.

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.

The AASLD/IDSA guidelines have specific recommendations for patients who have compensated cirrhosis and those with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C).¹⁶⁴

The guidelines state patients with decompensated cirrhosis should be referred for consideration for liver transplantation (Class 1, Level C.) The recommended regimen for patients with HCV genotype 1 or 4 who have decompensated cirrhosis (CTP class B or C), including those with hepatocellular carcinoma, is ledipasvir/sofosbuvir (Harvoni) and ribavirin for 12 weeks (Class IIb, Level C). For patients with HCV genotype 1 or 4 who have decompensated cirrhosis and anemia or ribavirin intolerance, ledipasvir/sofosbuvir (Harvoni) for 24 weeks is recommended (Class IIb, Level C). For patients with HCV genotype 1 or 4 who have decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed, ledipasvir/sofosbuvir (Harvoni) plus ribavirin for 24 weeks is an alternative regimen (Class IIb, Level C). For genotypes 2 or 3 patients with decompensated cirrhosis, the recommendation is sofosbuvir and weight based ribavirin (with consideration of the patient's renal function and hemoglobin level) for up to 48 weeks (Class IIb, Level B). The guidelines also recommend that both of these regimens should be used only by highly experienced HCV practitioners.

The guidelines further state that patients with decompensated cirrhosis should not receive any interferon-based regimen, monotherapy with PEG, RBV, or a DAA, any of the three currently approved protease inhibitors, or paritaprevir, ombitasvir, or dasabuvir based regimens. (Class III, Level A).

Other

The safety and efficacy of interferon alfa, alone or in combination with ribavirin, for the treatment of chronic HCV infection in liver or other organ transplant recipients has not been established.

The safety and efficacy of telaprevir (Incivek) in solid organ transplant recipients has not been established.

The safety and efficacy of boceprevir (Victrelis) alone, simeprevir (Olysio) alone, or either drug in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection in liver or other organ transplant recipients have not been studied.

The safety and efficacy of simeprevir in combination with peginterferon alfa and ribavirin has not been established in patients with HCV genotypes other than genotype one.¹⁶⁵

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.¹⁶⁶

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 three 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 percent 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.

The AASLD/IDSA guidelines provide treatment recommendations for treatment-naïve patients who develop recurrent HCV after liver transplantation.¹⁶⁷ These recommended regimens include ledipasvir/sofosbuvir (Harvoni) and weight-based ribavirin for 12 weeks for patients with HCV genotype 1 or 4 infection in the allograft (Class I, Level B). An alternate regimen listed for patients who are ribavirin ineligible or intolerant with HCV genotype 1 or 4 in the allograft liver includes ledipasvir/sofosbuvir (Harvoni) for 24 weeks (Class I, Level B). An alternative regimen for patients with HCV genotype 1 in the allograft 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-F2 due to HCV genotype 1 in the allograft is ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak) plus weight-based ribavirin for 24 weeks (Class I, Level B). Monotherapy with peginterferon, ribavirin, or a DAA is not recommended. In addition, any telaprevir (Incivek) or boceprevir (Victrelis)-based regimens are not recommended by the guidelines for treatment-naïve patients with compensated allograft HCV.

The AASLD/IDSA recommended regimen for patients with HCV genotype 2 or 3 in the allograft, including compensated cirrhosis, is sofosbuvir plus weight-based ribavirin for 24 weeks (Class IIb, Level C; Class I, Level B). The recommended regimen for patients with decompensated cirrhosis (Child Turcotte Pugh class B or C) due to HCV genotype 3 in the allograft is sofosbuvir plus low initial dose ribavirin (increased as tolerated) for 24 weeks (Class I, Level B). Treatment-naïve patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis according to the guidelines (Class 1, Level C).

DOSAGES

Combination Therapy

The AASLD/IDSA guidelines recommend combination therapy for the treatment of all HCV patients. The guidelines state there is no role for telaprevir (Incivek) or boceprevir (Victrelis) for any HCV patient. For regimens containing simeprevir (Olysio) with PEG/RBV, the total duration of therapy depends on viral response, as measured at week 4 or any week thereafter. Ledipasvir/sofosbuvir (Harvoni), ombitasvir/paritaprevir/ritonavir + dasabuvir (Viekira Pak), and sofosbuvir (Sovaldi) 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 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 Oral solution: 40 mg/mL
ribavirin (RibaPak)		Unit Dose Packs: <ul style="list-style-type: none"> ▪ 400-400 (56 X 400 mg tablets) ▪ 400-600 (28 X 400 mg + 28 X 600 mg tablets) ▪ 600-600 (56 X 600 mg tablets)
ribavirin (Ribasphere)		Capsule: 200 mg Tablets: 400, 600 mg
ribavirin (Moderiba)		Tablets: <ul style="list-style-type: none"> ▪ 200 mg tablet ▪ 600 mg Dose Pack Tablets ▪ 800 mg Dose Pack Tablets ▪ 1,000 mg Dose Pack Tablets ▪ 1,200 mg Dose Pack Tablets

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.

Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Dual Combination Therapy			
interferon alfacon-1 + ribavirin (Infergen) ¹⁶⁸	15 mcg SC daily plus ribavirin (1,000 mg per day if <75 kg or 1,200 mg per day if ≥75 kg)	48 weeks	Single Dose Vial (SDV): 9 mcg/0.3 mL, 15 mcg/0.5 mL
peginterferon alfa-2a (PEGASYS) + ribavirin ¹⁶⁹	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: 180 mcg/0.5 mL, 135 mcg/0.5 mL
	Genotypes 2, 3: 180 mcg SC once weekly plus ribavirin 400 mg twice daily	24 weeks	Convenience packs 4 SDV: 180 mcg/1 mL (with syringes) 4 prefilled syringes: 180 mcg/0.5 mL
	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 two divided doses	Genotype 1: 48 weeks Genotypes 2&3: 24 weeks	
peginterferon alfa-2b (PEGIntron) + ribavirin ¹⁷⁰	Age ≥18 years: 1.5 mcg/kg SC once weekly plus ribavirin 800 to 1,400 mg per day, based on body weight, in two divided doses Age 3–17 years: 60 mcg/m ² /week plus ribavirin 15 mg/kg/day orally with food in two divided doses Patients who reach their 18th birthday while receiving therapy should remain on the pediatric dosing regimen.	Genotype 1: 48 weeks Genotypes 2 & 3: 24 weeks Retreatment of prior treatment failure: 48 weeks, for all genotypes.	SDV: powder for injection (with diluent and syringes) 50, 80, 120, 150 mcg Redipen: 50, 80, 120, 150 mcg/0.5 mL
Triple Combination Therapy			
boceprevir† (Victrelis) + peginterferon/ribavirin ¹⁷¹	800 mg administered orally three times daily (every 7 - 9 hours) with food (a meal or light snack); therapy is initiated after 4 weeks of peginterferon and ribavirin therapy	24 – 44 weeks in combination with peginterferon and ribavirin	200 mg capsule
telaprevir* (Incivek) + peginterferon/ribavirin ¹⁷²	1,125 mg administered orally twice daily (10-14 hours apart) with food (not low fat)	12 weeks in combination with peginterferon and ribavirin	375 mg tablet
sofosbuvir (Sovaldi) + peginterferon/ribavirin ¹⁷³	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

†Manufacturing and distribution of boceprevir will be discontinued in the United States as of December 2015.

*Sales and distribution of telaprevir were discontinued in the U.S. as of October 16, 2014.

Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Triple Combination Therapy (continued)			
simeprevir (Olysio) plus peginterferon/ribavirin ¹⁷⁴	150 mg daily with food plus weekly peginterferon and weight-based ribavirin (1,000 mg per day if <75 kg or 1,200 mg per day if ≥75 kg)	Genotype 1 (treatment naïve and prior relapsers): 12 weeks in combination with peginterferon and ribavirin. Therapy is continued with peginterferon and ribavirin beyond the 12 weeks for a total of 24 weeks of treatment. Genotype 1 (prior non-responders): 12 weeks in combination with peginterferon and ribavirin. Therapy is continued with peginterferon and ribavirin beyond the 12 weeks for a total of 48 weeks of treatment.	150 mg capsule
Oral Combination Therapy			
ledipasvir/sofosbuvir (Harvoni) ¹⁷⁵	Fixed dose combination: ledipasvir 90 mg/sofosbuvir 400 mg orally once daily	Genotype 1 – treatment naïve (with or without cirrhosis): 12 weeks** Genotype 1 – treatment experienced (without cirrhosis): 12 weeks Genotype 1 – treatment experienced with cirrhosis: 24 weeks	90 mg/400mg fixed-dose tablet
ombitasvir, paritaprevir, ritonavir plus dasabuvir (Viekira Pak) ± ribavirin ^{176#}	Combination: two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) 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 cirrhosis): 24 weeks in combination with ribavirin^ Genotype 1b (without cirrhosis): 12 weeks Genotype 1b (with cirrhosis): 12 weeks in combination with ribavirin	ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg fixed-dose tablet, dasabuvir 250 mg tablet

Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
Oral Combination Therapy (continued)			
sofosbuvir (Sovaldi) plus ribavirin ¹⁷⁷	sofosbuvir 400 mg orally once daily plus weight-based ribavirin (<75 kg=1,000 mg and ≥75 kg=1,200 mg)	Genotype 2: 12 weeks Genotype 3: 24 weeks Patients with HCC 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) ¹⁷⁸	sofosbuvir 400mg orally once daily plus simeprevir 150 mg orally once daily	Genotype 1 (without cirrhosis): 12 weeks Genotype 1 (with cirrhosis): 24 weeks	400mg tablet, 150 mg capsule

**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.

^Viekira Pak 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).

#Viekira Pak: 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 with ribavirin is 24 weeks.

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 percent of participants entering the investigation. Due to the chronic nature, course of disease progression, and treatment duration for hepatitis C, most of the comparative trial data involve study designs that lack blinding. 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.

peginterferon alfa-2b (PEGIntron) + ribavirin versus peginterferon alfa-2a (PEGASYS) plus ribavirin in early virological response at 12 weeks

A randomized Romanian trial compared the efficacy of two peginterferons plus ribavirin with early virologic response (EVR) in 116 patients with chronic hepatitis C.¹⁷⁹ Patients were given peginterferon alfa-2a (PEGASYS) 180 mcg weekly plus ribavirin or peginterferon alfa-2b (PEGIntron) 1.5 mcg/kg weekly plus ribavirin. Ribavirin was dosed according to body weight. The patient population had treatment-naïve patients, as well as relapsers and nonresponders. The PEG-Intron group had more relapsers and nonresponders. EVR was assessed after 12 weeks of therapy and was defined as at least 2-log_{10} reduction in viral load from baseline. The EVR at 12 weeks was 82.2 percent and 67.2 percent for the PEGASYS and PEG-Intron groups, respectively ($p=0.08$). There were no significant differences in EVR between the two groups for the treatment-naïve patients (89.6 versus 75.2 percent, $p=0.61$). No significant differences in EVR were noted for the relapsers or the nonresponders either. This study lacked blinding and enrolled a heterogeneous patient population.

Peginterferon alfa-2a (PEGASYS) 180 mcg weekly and peginterferon alfa-2b (PEGIntron) 1.5 mcg/kg weekly, both with ribavirin, were compared in an open-label trial evaluating the early virologic response at 12 weeks in 385 adults with chronic hepatitis C genotype 1 with high viral loads.¹⁸⁰ Patients weighing less than 75 kg received ribavirin 1,000 mg daily, and patients weighing more than 75 kg received 1,200 mg daily. Five patients that were randomized did not receive any study drug. Therefore, only 380 patients were included in the intent-to-treat analysis. The mean HCV RNA levels were similar in both peginterferon groups throughout the study period. The early virologic response rate was defined as $> 2\text{-log}_{10}$ reduction in HCV-RNA concentration at week four or undetectable HCV-RNA at week 12. EVR was achieved in 66 percent of the peginterferon alfa-2a (PEGASYS) group and 63 percent of the peginterferon alfa-2b (PEGIntron) group. Patients on peginterferon alfa-2b (PEGIntron) plus ribavirin had a higher rate of discontinuation due to adverse effects (5.7 percent versus 1 percent). The study concluded that a substantial percentage of patients infected with HCV genotype 1 and high viral load can achieve EVR when treated with peginterferon and ribavirin.

A prospective, non-randomized, open-label trial performed in Spain enrolled 183 treatment-naïve patients with chronic hepatitis C.¹⁸¹ Patients were given peginterferon alfa-2a plus ribavirin or peginterferon alfa-2b plus ribavirin. SVR rates were similar with 65.9 percent and 62 percent ($p=0.64$) of patients receiving peginterferon alfa-2a and peginterferon alfa-2b, respectively, without differences according to genotype. In the patients with HCV genotype 1 ($n=117$), the SVR rates were 50.8 percent and 46.6 percent of patients receiving peginterferon alfa-2a and peginterferon alfa-2b, respectively ($p=0.713$). Rapid virological response at four weeks, early virological response at 12 weeks, and transient virological response were also similar. The rate of withdrawals due to treatment-related adverse events was 13.2 and 10.9 percent of patients in the peginterferon alfa-2a and peginterferon alfa-2b, respectively. The number of patients requiring dose modifications was similar in both groups. Authors concluded that peginterferons plus ribavirin have similar efficacy due to similar SVR rates.

peginterferon alfa-2a (PEGASYS) plus ribavirin (Copegus) versus peginterferon alfa-2b (PEG-Intron) plus ribavirin (Rebetol) for 48 weeks

The Individualized Dosing Efficacy versus Flat Dosing to Assess Optimal Peginterferon Therapy (IDEAL) study was a randomized, open-label trial comparing peginterferon alfa-2b (PEG-Intron) with ribavirin (Rebetol) and peginterferon alfa-2a (PEGASYS) with ribavirin (Copegus) in treatment-naïve patients with chronic hepatitis C genotype 1.^{182,183} Two comparisons were evaluated in the study: peginterferon alfa-2b 1 mcg/kg weekly plus ribavirin 800 to 1,400 mg daily (low dose peginterferon group, n=1,016) versus peginterferon alfa-2b 1.5 mcg/kg weekly plus ribavirin 800 to 1,400 mg daily (standard dose peginterferon group, n=1,019) and peginterferon alfa-2b 1.5 mcg/kg weekly plus ribavirin 800 to 1,400 mg daily versus peginterferon alfa-2a 180 mcg weekly plus ribavirin 1,000 to 1,200 mg daily (n=1,035). Ribavirin dosing for the peginterferon alfa-2b was according to FDA-approved labeling. Weight-based ribavirin dosing for use with peginterferon alfa-2a was not FDA-approved when the study was initiated. Therefore, ribavirin dosing with for the peginterferon alfa-2a group was calculated to deliver a mean of 13 mg/kg/day on the basis of data derived from previous trials and from the product information from the European Medicines Agency. All treatments were 48 weeks in duration followed by 24 weeks of follow-up observation. All groups had similar baseline characteristics including baseline HCV RNA levels, body weight, and African American race. The primary endpoint of SVR was similar among the groups in the intent-to-treat population with 39.8, 38, and 40.9 percent of patients achieving SVR in peginterferon alfa-2b 1.5 mcg/kg - RBV group, peginterferon alfa-2b 1 mcg/kg - RBV group, and peginterferon alfa-2a - RBV group, respectively (all p=NS). At the end of treatment (48 weeks), peginterferon alfa-2a with ribavirin had a higher response rate at 64.4 percent compared to 53.2 and 49.2 percent, respectively for peginterferon alfa-2b 1.5 mcg/kg with ribavirin and peginterferon alfa-2b 1 mcg/kg with ribavirin (standard dose peginterferon versus low dose peginterferon alfa-2b, p=0.04; standard dose peginterferon alfa-2b versus peginterferon alfa-2a, p<0.001). Relapse rate was also higher with peginterferon alfa-2a (31.5 percent) compared to 23.5 percent with standard dose peginterferon alfa-2b (8 percent difference, 95% CI, -13.2 to -2.8) and 20 percent with low dose peginterferon alfa-2b (standard dose peginterferon versus low dose peginterferon, 3.5 percent difference (95% CI, -1.6% to 8.6%). Due to the differences in FDA-approved ribavirin regimens, there are some notable differences among the groups in regards to ribavirin dosing and dosing adjustments. The mean ribavirin dose was significantly lower in the peginterferon alfa-2b groups (standard dose: 12.4 mg/kg/day; low dose: 12.6 mg/kg/day) compared to peginterferon alfa-2a (13.4 mg/kg/day) (p<0.001 for standard dose peginterferon alfa-2b group versus peginterferon alfa-2a; p<0.001 for low dose peginterferon alfa-2b versus peginterferon alfa-2a groups). The peginterferon alfa-2a arm had greater dose reductions for adverse effects compared to the peginterferon alfa-2b arms per the approved labeling. Dose reductions with ribavirin were required prior to the administration of erythropoietin for the treatment of ribavirin-related anemia. Overall, adverse effects reported were similar among the three groups. Discontinuation rates were 13, 10, and 13 percent for low dose peginterferon alfa-2b, standard dose peginterferon alfa-2b, and peginterferon alfa-2a, respectively. The manufacturer of PEG-Intron supported the study.

An Italian clinical trial compared the safety and efficacy of peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C.¹⁸⁴ Patients were treatment-naïve and were stratified by HCV genotype. Treatment duration was 24 or 48 weeks depending on HCV genotype. Patients were randomized to peginterferon alfa-2a 1.5 mcg/kg/week plus ribavirin 800 to 1,200 mg per day (n=212) or peginterferon alfa-2b 180 mcg/week plus ribavirin 800 to

1,200 mg per day (n=219). Baseline characteristics were similar between the two groups. By intention to treat, the two groups showed similar rates of treatment-related serious adverse events (both one percent) and discontinuation rates for adverse effects (seven versus six percent, respectively). Overall, SVR was higher in the peginterferon alfa-2a group than in the peginterferon alfa-2b group (66 percent versus 54 percent, respectively, $p=0.02$). For HCV genotypes 1 and 4, the SVR was 48 percent versus 32 percent, respectively ($p=0.04$). For the 143 patients with genotype 2, the SVR was 96 percent versus 82 percent, respectively ($p=0.01$).

In an Italian study of 320 consecutive, treatment-naïve patients with chronic hepatitis C, peginterferon alfa-2a 180 mcg weekly and peginterferon alfa-2b 1.5 mcg/kg weekly plus ribavirin were compared. Ribavirin was administered based on body weight. Duration of therapy was determined by genotype with genotypes 1 or 4 requiring 48 weeks of therapy and genotypes 2 and 3 requiring 24 weeks of therapy.¹⁸⁵ The primary outcome was SVR. Overall SVR were higher with peginterferon alfa-2a group (68.8 percent) compared to peginterferon alfa-2b (54.4 percent; $p=0.008$). Higher SVR rates were obtained in peginterferon alfa-2a than peginterferon alfa-2b among patients with genotype 1/4 (54 percent versus 39.8 percent; $p=0.04$), with genotype 2/3 (88.1 percent versus 74.6 percent; $p=0.046$), without cirrhosis (75.6 percent versus 55.9 percent; $p=0.005$), and with baseline levels HCV RNA >500,000 IU/mL (69 percent versus 46.2 percent; $p=0.002$). SVR rates in the two groups were not statistically different among patients with baseline HCV RNA \leq 500,000 IU/mL (68.4 percent versus 65.7 percent; $p=0.727$) or in patients with cirrhosis (42.4 percent versus 46.1 percent; $p=0.774$).

In an open-label, Egyptian trial, peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin were compared in 117 patients with chronic hepatitis C with genotype 4.¹⁸⁶ Patients were randomized to receive a weekly dose of peginterferon alfa-2a 180 mcg or peginterferon alfa-2b 1.5 mg/kg/week and a daily dose of ribavirin of 1,000-1,200 mg for 48 weeks. Overall SVR was 59.9 percent. SVR rate for peginterferon alfa-2a (70.6 percent) were higher than for peginterferon alfa-2b (54.6 percent; $p=0.017$). Relapse rates were significantly lower with peginterferon alfa-2a (5.1 versus 15.7 percent; $p=0.0019$). Tolerability was similar.

peginterferon alfa-2a (PEGASYS) plus ribavirin (Copegus) versus peginterferon alfa-2b (PEG-Intron) plus ribavirin (Rebetol) for 48 weeks in chronic hepatitis C/HIV co-infected patients

In a prospective, randomized, open-label study, the efficacy and safety of peginterferon alfa-2b weight based dosing (80 to 150 mcg/week) and peginterferon alfa-2a 180 mcg/kg/week for 48 weeks were compared in 182 patients co-infected with HCV and HIV.¹⁸⁷ Patients were treatment-naïve for HCV therapy. All patients received ribavirin 800 to 1,200 mg daily for 48 weeks. Overall, SVR rates were 42 percent for peginterferon alfa-2b and 46 percent for peginterferon alfa-2a ($p=0.65$). For genotypes 1 and 4, SVRs rates were 28 percent versus 32 percent ($p=0.67$) for peginterferon alfa-2b and peginterferon alfa-2a, respectively. For genotypes 2 and 3, SVR rates were 62 percent and 71 percent ($p=0.6$) for peginterferon alfa-2b and peginterferon alfa-2a, respectively. At 12 weeks, EVR was 70 percent in peginterferon alfa-2b group and 80 percent in the peginterferon alfa-2a group ($p=0.13$). Discontinuation due to adverse effects occurred in eight percent on peginterferon alfa-2b and 13 percent on peginterferon alfa-2a ($p=0.47$).

interferon alfacon-1 (Infergen) versus interferon alfacon-1 (Infergen) plus ribavirin

Forty treatment-naïve subjects with chronic hepatitis C were randomized to two treatment groups: interferon alfacon-1 9 mcg daily or interferon alfacon-1 9 mcg daily plus ribavirin 1,000 or 1,200 mg daily.¹⁸⁸ All subjects received 48 weeks of open-label therapy except for non-genotype 1 subjects in the combination treatment group, who received only 24 weeks of therapy. The proportion of subjects with genotype 1 infection was approximately 50 percent in each group. SVR was exhibited in 20 and 40 percent of subjects in the monotherapy and combination therapy groups, respectively (p=NS). For patients with genotype 1, SVR was 10 and 18 percent in the monotherapy and combination therapy groups, respectively (p=NS). Study discontinuations due to adverse events related to study drug were 20 and 25 percent, respectively. A total of four serious adverse events occurred, two in each treatment group, only one of which was determined to be study drug-related.

boceprevir (Victrelis) and peginterferon plus ribavirin

A randomized, double-blind study (SPRINT-2) evaluated the addition of boceprevir to peginterferon-ribavirin for the treatment of HCV genotype 1 in previously untreated adults.¹⁸⁹ All patients received peginterferon alfa-2b 1.5 mcg/kg weekly and ribavirin with weight-based dosing for the initial four weeks. Group 1 received placebo in addition to peginterferon + ribavirin for 44 weeks. Group 2 received boceprevir plus peginterferon + ribavirin for 24 weeks, and those with a detectable HCV RNA level between weeks eight and 24 received placebo plus peginterferon + ribavirin for an additional 20 weeks. Group 3 received boceprevir plus peginterferon + ribavirin for 44 weeks. A total of 938 non-Black and 159 Black patients were treated. In the non-Black population, the SVR was 40 percent in group 1 (125/311 patients), 67 percent in group 2 (211/316 patients; p<0.001), and 68 percent in group 3 (213/311 patients; p<0.001). In the Black cohort, the SVR was 23 percent in group 1 (12/52 patients), 42 percent in group 2 (22/52 patients; p=0.04), and 53 percent in group 3 (29/55 patients; p=0.004). SVR were similar for patients receiving boceprevir for 24 and 44 weeks. For patients in group 2, 44 percent of patients received peginterferon-ribavirin for 28 weeks. Dose reductions due to anemia occurred in 13 and 21 percent of group 1 and boceprevir-treated patients, respectively. The manufacturer of boceprevir supported the study.

In a randomized, double blind clinical trial (RESPOND-2), the effect of the combination of boceprevir and peginterferon + ribavirin was assessed in patients with chronic HCV genotype 1 who had previously been treated.¹⁹⁰ All patients received peginterferon alfa-2b 1.5 mcg/kg weekly and ribavirin with weight-based dosing for the initial four weeks. Patients were then randomized to placebo plus peginterferon + ribavirin (group 1) for 44 weeks, group 2 received boceprevir plus peginterferon + ribavirin for 32 weeks, and patients with a detectable HCV RNA at week eight received placebo plus peginterferon + ribavirin for an additional 12 weeks, and group 3 received boceprevir plus peginterferon + ribavirin for 44 weeks. A total of 403 patients were treated. SVR was achieved in 59 percent of group 2 and 66 percent of group 3 (both boceprevir groups p<0.001) compared to 21 percent in the control group or group 1. Among patients with an undetectable HCV RNA level at week eight, the rate of SVR was 86 percent after 32 weeks of triple therapy and 88 percent after 44 weeks of triple therapy. For patients (n=102) with a decrease of < 1-log₁₀ HCV RNA at treatment week 4, SVR rates were zero percent for the control group (group 1), 33 percent and 34 percent for group 2 and 3, respectively. Anemia was significantly more common in the groups receiving boceprevir than in the control group. The manufacturer of boceprevir supported the study.

telaprevir (Incivek) and peginterferon plus ribavirin¹⁹¹

A randomized, double-blind study (ADVANCE) evaluated the addition of telaprevir (Incivek) for the first eight or 12 weeks of peginterferon-ribavirin for the treatment of HCV genotype-1 in previously untreated adults.¹⁹² All patients received peginterferon alfa-2a 180 mcg weekly and ribavirin with weight-based dosing. Group 1 received telaprevir (Incivek) in addition to peginterferon + ribavirin for eight weeks followed by peginterferon + ribavirin for a total of 24 or 48 weeks. Group 2 received telaprevir (Incivek) plus peginterferon + ribavirin for 12 weeks, followed by peginterferon + ribavirin for a total of 24 or 48 weeks. Patients with undetectable HCV-RNA at four and 12 weeks (extended virologic response, eRVR) were treated for a total of 24 weeks; those who did not have undetectable HCV-RNA at both four and 12 weeks received peginterferon + ribavirin for 48 weeks. Group 3 was treated with placebo plus peginterferon + ribavirin for 12 weeks followed by interferon + ribavirin for a total course of 48 weeks. A total of 1,088 subjects were enrolled; nine percent were Black. The overall SVR was 72 percent in group 1, 79 percent in group 2, and 46 percent in group 3. Overall SVR was obtained in 62 percent (16/26) of Black patients. Group 2 had higher SVR rates among subjects with demographic or disease characteristics associated with poorer response compared to group 1. More patients in group 1 experienced virologic breakthrough after week 12 while receiving peginterferon + ribavirin (16 percent) than those in Group 2 (10 percent). Obtaining an eRVR predicted SVR. An eRVR was obtained in 58 percent of Group 2 patients versus eight percent of control group patients. Of those with an eRVR, 92 percent (195/212) of Group 2 patients and 93 percent (27/29) of group 3 patients achieved a SVR. Of patients who did not obtain an eRVR, extending the duration of peginterferon + ribavirin to 48 weeks resulted in higher SVR rates (61 percent of group 2 patients and 42 percent of control patients in this subgroup obtained a SVR). On treatment virologic failure and relapse occurred in seven and four percent, respectively of Group 2 patients compared to 29 and 24 percent of control patients.

A randomized, open-label, supportive clinical trial (ILLUMINATE), compared the SVR rates in treatment-naïve patients achieving eRVR when treated with 12 weeks of telaprevir in combination with peginterferon + ribavirin for either 24 weeks or 48 weeks. A total of 540 subjects were enrolled. A total of 352 (65 percent) achieved eRVR and of those, 322 (60 percent) were then randomized to either 24 weeks (n=162) or 48 weeks (n=160) of peginterferon + ribavirin. The SVR rates were 92 percent in the 24 week group versus 90 percent in the 48 week group. In the subgroup with cirrhosis at baseline (n=61), 30 patients achieved an eRVR and were randomized to either 24 (n=18) or 48 (n=12) weeks of peginterferon + ribavirin. The SVR rates in these patients were 67 percent (12/18) in the 24 week treatment group versus 92 percent (11/12) in the 48 week treatment group.

A randomized, double blind, placebo-controlled study (REALIZE) was conducted in 662 previously treated adults.¹⁹³ Patients were enrolled if they were a prior relapser (HCV-RNA undetectable at end of treatment following a peginterferon + ribavirin regimen but HCV-RNA detectable within 24 weeks of follow-up), a prior null responder (those that achieved a $<2\text{-log}_{10}$ drop in HCV-RNA level at week 12 of prior therapy), or a prior partial responder (achieved $\geq 2\text{-log}_{10}$ drop in HCV RNA at week 12 of prior therapy but never achieved undetectable HCV RNA while on treatment). Subjects were randomized 2:2:1 to one of two telaprevir containing arms (with and without a peginterferon + ribavirin four-week lead-in) or to a control group. Group 1 received telaprevir and peginterferon + ribavirin for 12 weeks followed by peginterferon + ribavirin for a total duration of 48 weeks. Group two received peginterferon + ribavirin for four weeks (lead-in), followed by telaprevir and peginterferon + ribavirin for 12 weeks, followed by peginterferon + ribavirin for a total duration of 48 weeks. Group 3 received

placebo + peginterferon + ribavirin for 16 weeks followed by peginterferon + ribavirin for a total duration of 48 weeks. There was no significant difference between groups 1 and 2 (with/without lead-in) in SVR rates, virologic failure, virologic breakthrough or relapse rates so the data were pooled. SVR rates in prior relapsers were 86 percent versus 22 percent for telaprevir-containing regimens and placebo-containing regimens, respectively. SVR rates in partial and null responders were 59 and 32 percent in group 1/2 versus 15 and five percent in the control group.

simeprevir (Olysio) and peginterferon plus ribavirin¹⁹⁴

The efficacy of simeprevir was tested in 785 treatment-naïve patients with HCV genotype 1 infection in two randomized, double-blind, placebo-controlled, multicenter, phase three trials (QUEST 1 and QUEST 2). The design of both trials was similar with all patients receiving 12 weeks of once-daily treatment with 150 mg of simeprevir or placebo, plus peginterferon alpha and ribavirin, followed by 12 or 36 weeks of therapy with peginterferon alpha and ribavirin in accordance with response guided therapy (RGT) criteria. The planned treatment duration was 24 weeks in patients who met the RGT treatment criteria of having a HCV RNA lower than 25 IU/mL (detectable or undetectable) at week four and also had undetectable HCV RNA at week 12. Patients who did not meet this criteria received 48 weeks of therapy. Patients in the control groups received 48 weeks of peginterferon alpha and ribavirin. Patients in QUEST 1 received peginterferon alpha 2a or 2b while patients in QUEST 2 received peginterferon alpha 2b. In the pooled analysis for QUEST 1 and QUEST 2, demographics and baseline characteristics were balanced between both trials and between the simeprevir and placebo treatment groups. The primary outcome of the study was the percentage of patients that had sustained virological response (SVR) which was defined as HCV RNA lower than 25 IU/mL detectable or undetectable 12 weeks after the planned end of treatment (SVR12).

In the pooled analysis of QUEST 1 and QUEST 2, 80 percent (419/521) of simeprevir-treated patients had an SVR compared to 50 percent (132/264) of the placebo, plus peginterferon alpha and ribavirin treated patients. Eighty-eight percent (459/521) of simeprevir-treated patients were eligible for total treatment duration of 24 weeks. In these patients, the SVR12 rate was 88 percent (405/459). In the simeprevir treatment group, SVR12 rates were lower in patients infected with genotype 1 virus with the NS3 Q80K polymorphism at baseline compared to patients infected with genotype 1 virus without the Q80K polymorphism.

The efficacy of simeprevir in treatment-experienced patients was established in the PROMISE trial. The PROMISE trial was a randomized, double-blind, placebo-controlled, multicenter, phase III trial in 393 patients with HCV genotype 1 infection who relapsed after prior interferon based therapy. All patients received 12 weeks of once daily treatment with 150 mg simeprevir or placebo, plus peginterferon alpha 2a and ribavirin, followed by 12 or 36 weeks of therapy with peginterferon alpha 2a and ribavirin therapy in accordance with the RGT criteria. Patients in the control group received 48 weeks of peginterferon alpha 2a and ribavirin. Demographics and baseline characteristics were balanced between the simeprevir and placebo treatment groups.

In PROMISE, 79 percent (206/260) of simeprevir -treated patients had an SVR compared to 37 percent (49/133) of the placebo plus peginterferon alpha and ribavirin treated patients. Ninety-three percent (241/260) of simeprevir treated patients were eligible for total treatment duration of 24 weeks. In these patients, the SVR12 rate was 83 percent (200/241). In the simeprevir treatment group, SVR12 rates were lower in patients infected with genotype 1a virus with the NS3 Q80K polymorphism at baseline compared to patients infected with genotype 1a virus without the Q80K polymorphism.

sofosbuvir (Sovaldi) and peginterferon plus ribavirin

NEUTRINO:¹⁹⁵ This open-label, single-arm trial evaluated triple therapy, sofosbuvir plus ribavirin plus peginterferon, in 327 treatment-naïve patients with genotype 1, 4, 5, or 6, of whom 98 percent had genotype 1 or 4. All patients received sofosbuvir, ribavirin, and peginterferon 180 mcg/week for 12 weeks. Overall SVR12 rate was reported in 90 percent of patients with genotypes 1 and 4 with a SVR breakdown of 89 percent, 92 percent, and 82 percent for genotype 1, 1a, and 1b. The SVR for genotype 4 was 96 percent. Treatment failure rate was nine percent, mostly due to relapse. Too few patients were included in the study with genotypes 5 and 6 to adequately evaluate efficacy. Cirrhosis and a non-CC IL28B genotype were strongly associated with a reduced response. No drug-resistance was detected in the 28 patients that relapsed.

sofosbuvir (Sovaldi) and ribavirin

POSITRON:¹⁹⁶ 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. Most patients had no prior HCV treatment (81 percent). 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 percent versus zero percent 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 percent, $p < 0.0001$). In addition, patients without cirrhosis had higher SVR12 compared to those with cirrhosis (81 versus 61 percent). The overall relapse rate was 20 percent, five percent of patients with genotype 2 relapsed and 38 percent with genotype 3. No virologic resistance was detected in patients who did not have a sustained virologic response.

FUSION:¹⁹⁷ 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. Approximately 25 percent of subjects had prior nonresponse to an interferon-based regimen, and 75 percent had prior relapse or breakthrough. The SVR12 rate was 50 percent in the 12 week group and 71 percent 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 four weeks resulted in an increased SVR12 rate for genotype 2 from 82 to 89 percent, and for genotype 3 from 30 to 62 percent. Relapse rate for genotype 2 was 18 and 11 percent, for 12 versus 16 weeks of therapy, respectively; relapse rate for genotype 3 was 66 and 38 percent, 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:¹⁹⁸ 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. The overall SVR12 rate was 67 percent in each treatment group; for those with genotype 2, 95 percent SVR12 was associated with sofosbuvir plus ribavirin, and 78 percent for peginterferon plus ribavirin; for those with genotype 3, 56 percent SVR12 was associated with sofosbuvir plus ribavirin and 63 percent 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 percent of patients were more common among patients receiving peginterferon than among those receiving sofosbuvir.

sofosbuvir (Sovaldi) and ribavirin pre-liver transplant

An open-label, phase 2 trial evaluated the efficacy of dual therapy, sofosbuvir plus ribavirin, for the prevention of HCV recurrence post-liver-transplant in patients with genotype 1 through 6 and hepatocellular carcinoma (HCC) who met the Milan criteria prior to transplantation.¹⁹⁹ Milan criteria was defined as the presence of a tumor 5 cm or less in diameter and no more than three tumor nodules, each 3 cm or less in diameter, and in subjects with multiple tumors. Prevention of post-transplantation reinfection was determined by measuring SVR at 12 weeks post-transplant (pTVR12= post-transplant virologic response). Patients had Child-Pugh-Turcotte (CPT) score ranging from 5 to 8 at baseline. Approximately 25 percent of patients were treatment-naïve. Eleven of 15 patients that received 24 weeks of therapy relapsed in the pre-transplant phase of the study, suggesting the need for a longer duration of treatment of up to 48 weeks. Thirty-six of 41 subjects that received treatment drug and underwent liver transplantation were follow to post-transplant week 12. Of these patients, 63.9 percent achieved sustained pTVR12. Twenty-four patients reached post-transplant week 24, of which 71 percent achieved sustained pTVR24.

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

PHOTON-1:²⁰⁰ This is an ongoing 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/mm³ or had virologically suppressed HIV-1 with a CD4+ cell count >200 cells/mm³. Efficacy data for 210 patients are reported. In the trial, 76 percent of genotype 1 HCV treatment-naïve patients receiving 24 weeks of therapy achieved a SVR 12. SVR12 for genotypes 2 and 3 was 88 and 92 percent, respectively. All patients in the study who did not achieve SVR12 had viral relapse after cessation of therapy, with the exception of two participants who were non-adherent to study drugs.

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.²⁰¹ 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 two. Overall, 16 percent 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 four groups were 99 percent (95% CI 96 to 100) for the 12 weeks of ledipasvir/sofosbuvir, 97 percent (95% CI 94 to 99) for the 12 weeks of ledipasvir/sofosbuvir plus ribavirin, 98 percent (95% CI 95 to 99) for the 24

weeks of ledipasvir/sofosbuvir and 99 percent (95% CI 97 to 100) for the 24 weeks of ledipasvir/sofosbuvir plus ribavirin. The SVR rates for all four treatment groups were statistically superior to the calculated historical SVR rate of 60 percent in this patient population ($p < 0.001$ for all comparisons). The SVR ranged from 94 to 100 percent in patients with cirrhosis, from 97 to 99 percent in patients with HCV genotype 1a infection, 97 to 99 percent among those with a non-CC *IL28B* allele, and 91 to 100 percent among black patients. There were a total of ten patients in the two 24-week groups who discontinued treatment prematurely due to adverse events and all ten of these patients had a SVR; the shortest duration of therapy among these patients was eight 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 two 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/sofosbuvir 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 four regimens evaluated.

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.²⁰² The 1:1:1:1 randomization arms were identical to ION-1 with four total groups, two 12-week treatment groups, one with and one without added ribavirin and two 24-week treatment groups, one with and one 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 four treatment arms. Overall, 52 percent of the enrolled patients had received prior treatment with a protease inhibitor regimen and 88 percent had the non-CC *IL28B* genotype. The primary efficacy endpoint was SVR12 with a secondary endpoint of SVR24. The SVR rates for the four groups were 94 percent (95% CI 87 to 97), for the 12 weeks of ledipasvir/sofosbuvir, 96 percent (95% CI 91 to 99) for the 12 weeks of ledipasvir/sofosbuvir plus ribavirin, 99 percent (95% CI 95 to 100) for the 24 weeks of ledipasvir/sofosbuvir and 99 percent (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 percent in this patient population ($p < 0.001$ for all comparisons). A total of 11 patients who were on one 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 twelve. 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 percent and 82 percent, respectively. The SVR rates for cirrhotic patients randomized to the two 24-week arms were 95 percent and 100 percent. 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, six percent of patients who received a 24-week therapy experienced a serious adverse event. These serious adverse effects included one 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 percent) than in the other three treatment groups (81 percent to 90 percent). Higher rates of constitutional and neuropsychiatric side effects were observed in the two groups that received the ribavirin-containing regimen than in the two 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 eight weeks, ledipasvir/sofosbuvir plus ribavirin for eight weeks or ledipasvir/sofosbuvir for twelve weeks.²⁰³ 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 percent in this population. A key secondary endpoint was the noninferiority of eight weeks of ledipasvir/sofosbuvir to the 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 ten 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 three treatment groups, with SVR rates superior to the adjusted historical control rate of 60 percent ($p < 0.001$ for all comparisons). The eight-week ledipasvir/sofosbuvir treatment arm had a 94 percent SVR12 rate (95% CI 90 to 97), the ledipasvir/sofosbuvir/ribavirin eight-week treatment arm had a 93 percent SVR12 rate (95% CI 89 to 96) and the twelve-week ledipasvir/sofosbuvir arm has a 95 percent SVR 12 rate (95% CI 92 to 98). In the secondary analysis of noninferiority, the rate of sustained virologic response among patients who received eight weeks of ledipasvir/sofosbuvir without ribavirin met the prespecified criteria for noninferiority compared to the response rates in the other two 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 eight weeks of ledipasvir/sofosbuvir ranged from 89 percent to 100 percent in all these subgroups. The baseline fibrosis score also had no discernible effect on the SVR12 rate. Five percent of patients in the eight-week ledipasvir/sofosbuvir group experienced a virologic relapse after the end of therapy as did four percent in the eight week ledipasvir/sofosbuvir/ribavirin group and one percent in the 12-week group. Fatigue, headache, and nausea were the most common adverse events. Although relapse was more common among patients who received eight 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 eight-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

SAPPHERE-I was an international phase 3, randomized, double blind, placebo-controlled trial involving 631 previously untreated patients with HCV genotype 1 infection.²⁰⁴ 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 percent in previously untreated patients without cirrhosis who received telaprevir/peginterferon/ribavirin. The SVR12 of the active treatment group was 96.2 percent (95% CI, 94.5 to 97.9), which was statistically superior to the historical control. The response rates were 95.3 percent among patients with HCV genotype 1a and 98 percent among patients with HCV genotype 1b infections. The SVR12 rates were similar regardless of baseline fibrosis score (97 percent for F0/F1, 94.3 percent for F2 and 92.5 percent 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 percent) had a relapse by post-treatment week twelve. Each of these eight patients had at least one amino acid variant known to confer resistance to one of the three direct acting antiviral agents included in the regimen. Modifications of the ribavirin dose due to adverse events occurred in 26 patients. The SVR 12 was 93.5 percent among patients who had a modification of the ribavirin dose and 96.4 percent 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

SAPPHERE-II was an international, randomized, placebo-controlled double blind phase 3 trial with an identical study design to SAPPHERE-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.²⁰⁵ 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 percent based on a retreatment regimen of peginterferon-ribavirin and telaprevir. The SVR12 for the active treatment group in this trial was 96.3 percent (95% CI, 94.2 to 98.4); superior to the historical control rate. Response rates of 95.3 percent, 100 percent and 95.2 percent were seen in patients with a prior relapse, a prior partial response and a prior null response, respectively. The two 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 percent versus 5.2 percent, $p=0.03$). A total of 2.4 percent 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).²⁰⁶ 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 two treatment arms. The primary endpoint was SVR12, which was compared to a historical response rate of 64 percent 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 percent (95% CI 92.8 to 100) and 100 percent 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 percent, 96 percent and 100 percent in prior null responders, partial responders and relapsed patients, respectively. SVR12 rates were 100 percent in all subgroups of the ribavirin-free arm. The most common adverse events in both groups were fatigue (31.9 percent and 15.8 percent) and headache (24.2 percent and 23.2 percent) 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 normal at the end of treatment was experienced more often by patients receiving ribavirin than those who did not receive ribavirin (42 percent versus 5.5 percent, respectively; $p < 0.001$).

Two phase 3, double blind, randomized, placebo-controlled trials were designed to evaluate the role of ribavirin in treatment-naïve HCV genotype 1 patients without cirrhosis (PEARL-III and PEARL-IV).²⁰⁷ 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) was 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 percent for HCV genotype 1a and 80 percent 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 percent (95% CI, 98.6 to 100) of patients receiving ribavirin achieved an SVR12 and 99 percent (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 percent (95% CI, 93.7 to 100) of patients receiving ribavirin achieved an SVR12 and 90.2 percent (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 two 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 percent) compared to the HCV genotype 1a group who did receive ribavirin (2 percent). 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 two 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 percent 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 percent of patients who received the ribavirin-free regimen ($p<0.001$). Similarly, in the genotype 1b study, 51.2 percent of patients who received ribavirin had a low hemoglobin level at the end of treatment as compared with 3.4 percent of patients who did not receive ribavirin ($p<0.001$).

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 III trial enrolling both untreated and previously treated adults ($n=380$) with HCV genotype 1 infection and compensated cirrhosis.²⁰⁸ 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 $60,000 \text{ mm}^3$, a serum albumin of $\geq 2.8 \text{ g/dL}$, a total bilirubin $< 3 \text{ g/dL}$, 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 one tablet once daily along with dasabuvir 250 mg twice daily and ribavirin administered at 1000 mg or 1200 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 percent (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 percent, (97.5% CI 87.6 to 96.1) of patients who were randomized to 12 weeks of treatment achieved a SVR12, while 95.9 percent (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 percent in the 12-week arm and 92.9 percent 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 percent (95% CI 2.7 to 9.2) versus 0.6 percent (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.

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.²⁰⁹ 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 percent were HCV treatment-naïve and 19 percent had compensated cirrhosis and 89 percent had HCV genotype 1a infection. The SVR12 rates were 91 percent (51/56 patients) in those patients with HCV genotype 1a infection and 100 percent (7/7) for patients with HCV 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 and dasabuvir (Viekira Pak) plus ribavirin in genotype 1 liver transplant patients

CORAL-1 was a phase 2, open-label trial assessing the safety and efficacy of co-formulated ombitasvir-ABT-450/r (25 mg/150 mg/100 mg) and dasabuvir (250 mg twice daily) with ribavirin (dosing at investigator's discretion) for 24 weeks in 34 liver-transplant recipients with recurrent HCV genotype 1 infections.²¹⁰ All enrolled patients had received a liver transplant due to chronic HCV infection at least 12 months prior. The median time since liver transplantation was 3.3 years. Patients could not have been treated with interferon-based regimens after liver transplantation occurred. Patients with Metavir scores of ≥ 3 were excluded. Patients were also required to be on a stable cyclosporine-based or tacrolimus-based immunosuppressive regimen prior to enrolling in the study. Blood levels of the calcineurin inhibitors (cyclosporine or tacrolimus) were monitored and dosages were modified to maintain therapeutic levels. The primary endpoint was SVR12 and secondary endpoints included the percentage of patients with an SVR24, virologic failure during treatment and post-treatment relapse. SVR12 was achieved in 33 of the 34 treated patients (95% CI, 85 to 100). The same percentage, 97 percent achieved an SVR24. The most common adverse events were fatigue, headache and cough. None of the patients experienced graft rejection. Grade 2 declines in hemoglobin levels occurred in nine patients and one patient had a grade 3 decline in hemoglobin level.

simeprevir (Olysio) plus sofosbuvir (Sovaldi) in genotype 1

The FDA approval for the combination of simeprevir plus sofosbuvir in chronic HCV genotype 1 patients was based on the COSMOS trial. COSMOS was a phase II, randomized, open-label multicenter trial enrolling patients with HCV genotype 1 with compensated liver disease. Patients were stratified into two cohorts. Cohort one (n=80) included patients who were previous non-responders to peginterferon and ribavirin who also had a Metavir score of F0-F2. Cohort two (n=87) consisted of patients who either were previous non-responders to peginterferon and ribavirin or who were treatment naïve and had documented severe liver fibrosis (Metavir score F3-F4). Patients were further stratified by genotype 1a versus other subtypes and the patient's IL28B genotype in cohort one. The study did not enroll patients with previous non-response to protease inhibitor therapy or NS5A inhibitors. Patients were randomized to one of four treatment groups. The four groups consisted of simeprevir and sofosbuvir with or without ribavirin for 24 or 12 weeks. The Q80K polymorphism was present in 45 percent of patients and this was not equally balanced across treatment groups. The overall SVR12 rate was 92 percent, cohort one had an SVR12 rate of 90 percent (95 % CI 81 to 96) and the SVR12 rate in cohort two was 94 percent (95% CI 87 to 98). The results were not significantly altered by the use of ribavirin, duration of treatment or by previous treatment status. The only baseline characteristic that notably affected virologic response was the age of participants 45 years or younger, which was associated with a disproportionate number of non-virologic failures. Ten patients (five in each of the 24-week cohorts) discontinued treatment prematurely; four of the withdrawals were due to adverse events. The most common adverse events were fatigue (31 percent), headache (20 percent), and nausea (16 percent). Grade 3 or 4 adverse events were reported in less than five percent of all patients, except increased blood amylase concentration, however, there were no cases of clinical pancreatitis. Six patients had viral relapse after the end of treatment, five of the six had developed resistance-associated mutations to simeprevir, but none to sofosbuvir. Five of the six patients were treated for 12 weeks including three patients with advanced fibrosis. The authors noted that a benefit from extending treatment to 24 weeks in at least a subset of patients could not therefore, be entirely ruled out. This supports the FDA indication of 24 weeks of treatment with simeprevir/sofosbuvir for patients with cirrhosis.

META-ANALYSIS

An adjusted indirect analysis evaluated randomized controlled trials with peginterferons with ribavirin when compared to conventional interferon with ribavirin for the treatment of chronic hepatitis C.²¹¹ The analysis found no statistically significant differences between combination therapy with ribavirin with peginterferon alfa-2a and peginterferon alfa-2b for SVR, discontinuations due to adverse effects, anemia, depression or flu-like symptoms. Closer evaluation of the studies did not reveal any difference in the result.

A systematic review evaluated the direct comparative randomized studies of the peginterferon alfa-2a and peginterferon alfa-2b to assess the benefits and harms of the two treatments.²¹² Searches were performed with the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and LILACS through July 2009. Twelve randomized clinical trials, including 5,008 patients, that compared peginterferon alpha-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin were identified. Overall, peginterferon alpha-2a significantly increased the number of patients who achieved SVR versus peginterferon alfa-2b in eight trials (47 percent versus 41 percent; risk ratio 1.11, 95% CI, 1.04 to 1.19;

p=0.004). Subgroup analyses of risk of bias, viral genotype, and treatment history yielded similar results. Discontinuations in 11 trials did not reveal any significant differences between the two peginterferons.

A systematic review examined SVR rates and long-term outcomes from randomized comparative antiviral drug trials in treatment-naïve patients.²¹³ Searches were performed using MEDLINE (1947 to August 2012), the Cochrane Library Database, EMBASE, Scopus, PsychINFO, and clinical trial registers. The authors identified no studies that included long-term outcomes so SVR was used as the primary outcome measure. Only key results are noted here. Dual therapy with peginterferon alfa-2b was slightly less effective in obtaining a SVR compared to peginterferon alfa-2a, RR 0.87 (95% CI, 0.80 to 0.95) with a pooled absolute difference of eight percentage points. Peginterferon alfa-2b showed a lower risk for serious adverse events but the differences were small (absolute difference one percent). In patients with genotype 2 or 3 HCV, standard doses and durations (24 weeks) of dual therapy were more effective when compared to the lower dosage or shorter duration therapies. In patients with genotype 1 HCV, triple therapy, with the inclusion of boceprevir (2 studies) or telaprevir (Incivek) (4 studies), was associated with a higher rate of SVR than dual therapy. The absolute difference was 22 to 31 percentage points. Triple therapy was also associated with a shorter duration of treatment compared to dual therapy. However, boceprevir was associated with a higher risk of hematologic adverse events (neutropenia, anemia, and thrombocytopenia) and telaprevir (Incivek) was associated with an increased risk of anemia and rash compared to dual therapy. The authors did note that a Veterans Affairs cohort study found SVR to be associated with a 30 to 50 percent reduction in mortality risk after adjustment for cofounders.

SUMMARY

Therapy for chronic hepatitis C virus (HCV) has evolved substantially in the last two decades since interferon-alpha was first approved for this indication. Genotype 1 accounts for about 70 to 75 percent of the HCV cases in the United States. Monotherapy with interferon resulted in sustained virologic responses (SVR) of approximately 10 to 20 percent 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 percent and remained the standard of care for many years; however, this regimen was not well tolerated as interferon therapy is associated with severe symptoms, including influenza-like illness, neuropsychiatric symptoms, and ribavirin is associated with anemia. In 2011, the standard of care changed with the introduction of the first direct acting antivirals (DAAs), the NS3/4A protease inhibitors boceprevir (Victrelis) and telaprevir (Incivek). Triple therapy with one of these protease inhibitors, peginterferon, and ribavirin resulted in SVR rates of 60 to 80 percent in genotype 1 HCV patients. An additional NS3/4A protease inhibitor, simeprevir (Olysio), was approved in 2013. Simeprevir (Olysio) 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 (Olysio) is still associated with many drug interactions and has similar genotype coverage and resistance profiles to telaprevir (Incivek) and boceprevir (Victrelis). In addition, patients prescribed simeprevir (Olysio) 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 (Olysio), 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 (Sovaldi) represents a new class of DAA as a HCV nucleotide analog NS5B polymerase inhibitor. It is indicated as part of a triple therapy regimen for treatment-naïve patients with HCV genotypes 1 and 4, resulting in SVR rates of approximately 90 percent. In addition, sofosbuvir (Sovaldi) combined with ribavirin for the treatment of genotypes 2 and 3 represents the first all-oral regimen approved by the FDA for HCV therapy.

In 2014, there were FDA rulings that 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. 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. 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 percent or greater.

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) has published guidelines for testing, managing, and treating hepatitis C. This guidance defines 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) 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. For treatment naïve patients with HCV genotype 1, the recommendation is for any of the three newly approved all-oral treatment options (ledipasvir/sofosbuvir [Harvoni], ombitasvir/paritaprevir/ritonavir and dasabuvir [Viekira Pak] with or without ribavirin, or simeprevir plus sofosbuvir with or without ribavirin). Peginterferon and ribavirin with or without sofosbuvir, simeprevir, telaprevir, or boceprevir are no longer recommended by these guidelines for the treatment of patients with HCV genotype 1.

The HCV market is expected to grow, as there are more treatments in the pipeline with potential for future pangenotypic treatment protocols to be all-oral regimens. The newest wave of drugs represents an advance in the management of HCV with significant improvements in efficacy and tolerability.

REFERENCES

- 1 Infergen [package insert]. Warrendale, PA; Kadmon Pharmaceutical; December 2013.
- 2 PEGASYS [package insert]. South San Francisco, CA; Genentech Inc.; September 2014.
- 3 PEG-Intron [package insert]. Whitehouse Station, NJ; Schering; January 2015.
- 4 COPEGUS [package insert]. Nutley, NJ; Roche Pharmaceuticals; February 2013.
- 5 Rebetol [package insert]. Whitehouse Station, NJ; Schering; December 2014.
- 6 Ribasphere capsule [package insert]. Warrendale, PA; Kadmon Pharmaceutical; December 2014.
- 7 Ribasphere tablet [package insert]. Warrendale, PA; Kadmon Pharmaceutical; December 2014.
- 8 Ribapak [package insert]. Warrendale, PA; Kadmon Pharmaceutical; December 2014.
- 9 Moderiba [package insert]. North Chicago, IL; AbbVie, Inc; January 2014.
- 10 Victrelis [package insert]. Whitehouse Station, NJ; Merck & Co; July 2014.
- 11 Olysio [package insert]. Titusville, NJ; Janssen Therapeutics; November 2014.
- 12 Incivek [package insert]. Cambridge, MA; Vertex Pharmaceuticals Incorporated; October 2013.
- 13 Harvoni [package insert]. Foster City, CA; Gilead Sciences, Inc.; October 2014.
- 14 Sovaldi [package insert]. Foster City, CA; Gilead Sciences, Inc.; November 2014.
- 15 Harvoni [package insert]. Foster City, CA; Gilead Sciences, Inc.; October 2014.
- 16 Viekira Pak [package insert]. North Chicago, IL; AbbVie Inc.; January 2015.
- 17 Centers for Disease Control and Prevention: Hepatitis C Information for Health Professionals. Available at: <http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm#section1>. Accessed January 30, 2015.
- 18 Deming P, Mercier R, Pai, MP, Viral Hepatitis. In: DiPiro JT, ed. Pharmacotherapy A Pathophysiologic Approach. Mcgraw-Hill 7th ed; 2008;675-691.
- 19 Dienstag JL. Chapter 306. Chronic Hepatitis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 18e. New York: McGraw-Hill; 2012.
- 20 American Association for the Study of Liver Diseases, Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C Available at: <http://www.hcvguidelines.org/full-report/hcv-testing-and-linkage-care>. Accessed January 30, 2015.
- 21 US Preventive Services Task Force. Screening for hepatitis C virus infection in adults: US Preventive Services Task Force recommendation statement. <http://www.uspreventiveservicestaskforce.org/uspstf/uspshcpc.htm>. Accessed on January 30, 2015.
- 22 CDC. Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965. Available at <http://www.cdc.gov/mmwr/pdf/rr/rr6104.pdf>. Accessed February 9, 2015.
- 23 American Association for the Study of Liver Diseases, Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C Available at: <http://www.hcvguidelines.org/full-report/hcv-testing-and-linkage-care>. Accessed January 30, 2015.
- 24 Dienstag JL. Chapter 306. Chronic Hepatitis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 18e. New York: McGraw-Hill; 2012.
- 25 American Association for the Study of Liver Diseases, Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://www.hcvguidelines.org/full-report/hcv-testing-and-linkage-care> Accessed January 30, 2015.
- 26 Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, Management, and Treatment of Hepatitis C: An Update. Hepatology. 2009; April:1335-1374.
- 27 American Association for the Study of Liver Diseases/Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://www.hcvguidelines.org/full-report/when-and-whom-initiate-hcv-therapy>. Accessed January 30, 2015.
- 28 Chen J, Florian J, Carter W, et al. Earlier Sustained Virologic Response End Points for Regulatory Approval and Dose Selection of Hepatitis C Therapies Gastroenterology 2013;144:1450-1455.
- 29 Dienstag JL. Chapter 306. Chronic Hepatitis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 18e. New York: McGraw-Hill; 2012.
- 30 Dienstag JL. Chapter 306. Chronic Hepatitis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 18e. New York: McGraw-Hill; 2012.
- 31 American Gastroenterological Association Technical Review on the Management of Hepatitis C. Gastroenterol. 2006; 130:231-264.
- 32 Gerber L, Welzel TM, Zeuzem New therapeutic strategies in HCV: polymerase inhibitors Liver International 2013;85-92 doi: 10.1111/liv.12068.
- 33 Poordad F, McCone J, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011; 364(13):1195-1206.
- 34 Jacobson IR, McHutchison JG, Dusheiko G, et al for the ADVANCE Study Team. Telaprevir (Incivek) for Previously Untreated Chronic Hepatitis C Virus Infection. N Engl J Med. 2011; 364:2405-2416.
- 35 Clark VC, Peter JA, Nelson DR, et al. New therapeutic strategies in HCV: second-generation protease inhibitors. Liver Int 2013; 80-84 doi:10.1111/liv.12061.
- 36 American Association for the Study of Liver Diseases/Infectious Disease Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://hcvguidelines.org/full-report/introduction>. Accessed January 26, 2015.
- 37 American Association for the Study of Liver Diseases/Infectious Disease Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://hcvguidelines.org/full-report/when-and-whom-initiate-hcv-therapy>. Accessed January 26, 2015.
- 38 American Association for the Study of Liver Diseases, Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://hcvguidelines.org/full-report/initial-treatment-hcv-infection>. Accessed January 26, 2015.
- 39 American Association for the Study of Liver Diseases, Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://hcvguidelines.org/full-report/retreatment-persons-whom-prior-therapy-has-failed>. Accessed January 26, 2015.
- 40 American Association for the Study of Liver Diseases, Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://hcvguidelines.org/full-report/initial-treatment-hcv-infection>. Accessed January 30, 2015.
- 41 American Association for the Study of Liver Diseases, Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://hcvguidelines.org/full-report/retreatment-persons-whom-prior-therapy-has-failed>. Accessed January 26, 2015.
- 42 American Association for the Study of Liver Diseases, Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://hcvguidelines.org/full-report/initial-treatment-hcv-infection>. Accessed January 30, 2015.

- 43 American Association for the Study of Liver Diseases, Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://hcvguidelines.org/full-report/retreatment-persons-whom-prior-therapy-has-failed>. Accessed January 30, 2015.
- 44 American Association for the Study of Liver Diseases, Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://hcvguidelines.org/full-report/initial-treatment-hcv-infection>. Accessed January 30, 2015.
- 45 American Association for the Study of Liver Diseases, Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://hcvguidelines.org/full-report/retreatment-persons-whom-prior-therapy-has-failed>. Accessed January 30, 2015.
- 46 American Association for the Study of Liver Diseases, Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://hcvguidelines.org/full-report/initial-treatment-hcv-infection>. Accessed January 30, 2015.
- 47 American Association for the Study of Liver Diseases, Infectious Diseases Society of America: Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://hcvguidelines.org/full-report/retreatment-persons-whom-prior-therapy-has-failed>. Accessed January 30, 2015.
- 48 Reddy KR, Wright TL, Pockros PJ, et al. Efficacy and safety of pegylated (40-kd) interferon alpha-2a compared with interferon alpha-2a in noncirrhotic patients with chronic hepatitis C. *Hepatology*. 2001; 33:433–438.
- 49 Melian EB and Plosker GL. Interferon Alfacon-1: A Review of its Pharmacology and Therapeutic Efficacy in the Treatment of Chronic Hepatitis C. *Drugs*. 2001; 61:1661-1691.
- 50 Ribavirin. Available at: <http://www.clinicalpharmacology.com>. Accessed January 30, 2015.
- 51 Brok J, Gluud LL, Gluud C. Ribavirin monotherapy for chronic hepatitis C infection: a Cochrane Hepato-Biliary Group systematic review and meta-analysis of randomized trials. *Am J Gastroenterol*. 2006; 101(4):842-7.
- 52 Brok J, Gluud LL, Gluud C. Ribavirin monotherapy for chronic hepatitis C infection: a Cochrane Hepato-Biliary Group systematic review and meta-analysis of randomized trials. *Am J Gastroenterol*. 2006; 101(4):842-7.
- 53 Rebetol [package insert]. Whitehouse Station, NJ; Schering; December 2014.
- 54 Sovaldi [package insert]. Foster City, CA; Gilead Sciences, Inc.; November 2014.
- 55 Viekira Pak [package insert]. North Chicago, IL; AbbVie Inc.; January 2015.
- 56 Harvoni [package insert]. Foster City, CA; Gilead Sciences, Inc.; October 2014.
- 57 Viekira Pak [package insert]. North Chicago, IL; AbbVie Inc.; January 2015.
- 58 PEG-Intron [package insert]. Whitehouse Station, NJ; Schering; January 2015.
- 59 PEGASYS [package insert]. South San Francisco, CA; Genentech Inc.; September 2014.
- 60 Infergen [package insert]. Warrendale, PA; Three Rivers Pharmaceutical; July 2010.
- 61 PEGASYS [package insert]. South San Francisco, CA; Genentech Inc.; September 2014.
- 62 PEG-Intron [package insert]. Whitehouse Station, NJ; Schering; January 2015.
- 63 Victrelis [package insert]. Whitehouse Station, NJ; Merck & Co; July 2014.
- 64 Olysio [package insert]. Titusville, NJ; Janssen Therapeutics; November 2014.
- 65 Sovaldi [package insert]. Foster City, CA; Gilead Sciences, Inc.; November 2014.
- 66 Harvoni [package insert]. Foster City, CA; Gilead Sciences, Inc.; October 2014.
- 67 Viekira Pak [package insert]. North Chicago, IL; AbbVie Inc.; January 2015.
- 68 PEGASYS [package insert]. South San Francisco, CA; Genentech Inc.; September 2014.
- 69 PEG-Intron [package insert]. Whitehouse Station, NJ; Schering; January 2015.
- 70 Infergen [package insert]. Warrendale, PA; Three Rivers Pharmaceutical; July 2010.
- 71 Dalgard O, Bjoro K, Hellum K, et al. Thyroid dysfunction during treatment of chronic hepatitis C with interferon alpha: no association with either interferon dosage or efficacy of therapy. *J Intern Med*. 2002; 251:400-406.
- 72 Rebetol [package insert]. Whitehouse Station, NJ; Schering; December 2014.
- 73 Ribasphere [package insert]. Cranberry Twp, PA; Three Rivers Pharmaceuticals, September 2005.
- 74 COPEGUS [package insert]. Nutley, NJ; Roche Pharmaceuticals; February 2013.
- 75 Ribapak [package insert]. Warrendale, PA; Kadmon Pharmaceutical; December 2014.
- 76 Moderiba [package insert]. North Chicago, IL; AbbVie, Inc; January 2014.
- 77 Rebetol [package insert]. Whitehouse Station, NJ; Schering; December 2014.
- 78 Victrelis [package insert]. Whitehouse Station, NJ; Merck & Co; July 2014.
- 79 Incivek [package insert]. Cambridge, MA; Vertex Pharmaceuticals Incorporated; December 2012.
- 80 Olysio [package insert]. Titusville, NJ; Janssen Therapeutics; November 2014.
- 81 Sovaldi [package insert]. Foster City, CA; Gilead Sciences, Inc.; November 2014.
- 82 Harvoni [package insert]. Foster City, CA; Gilead Sciences, Inc.; October 2014.
- 83 Viekira Pak [package insert]. North Chicago, IL; AbbVie Inc.; January 2015.
- 84 FDA. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>. Accessed January 30, 2015.
- 85 Available at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/020903s048,021546s004ltr.pdf. Accessed January 30, 2015.
- 86 Available at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021511s024ltr.pdf. Accessed January 30, 2015.
- 87 Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>. Accessed January 30, 2015.
- 88 Victrelis [package insert]. Whitehouse Station, NJ; Merck & Co; July 2014.
- 89 Incivek [package insert]. Cambridge, MA; Vertex Pharmaceuticals Incorporated; December 2012.
- 90 PEGASYS [package insert]. South San Francisco, CA; Genentech Inc.; September 2014.
- 91 PEG-Intron [package insert]. Whitehouse Station, NJ; Schering; January 2015.
- 92 Victrelis [package insert]. Whitehouse Station, NJ; Merck & Co; July 2014.
- 93 Incivek [package insert]. Cambridge, MA; Vertex Pharmaceuticals Incorporated; December 2012.
- 94 Sovaldi [package insert]. Foster City, CA; Gilead Sciences, Inc.; November 2014.
- 95 Olysio [package insert]. Titusville, NJ; Janssen Therapeutics; November 2014.

- 96 Infergen [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; July 2010.
- 97 PEGASYS [package insert]. South San Francisco, CA; Genentech Inc.; September 2014.
- 98 PEG-Intron [package insert]. Whitehouse Station, NJ; Schering; January 2015.
- 99 Infergen [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; July 2010.
- 100 PEGASYS [package insert]. South San Francisco, CA; Genentech Inc.; September 2014.
- 101 PEGASYS [package insert]. South San Francisco, CA; Genentech Inc.; September 2014.
- 102 PEG-Intron [package insert]. Whitehouse Station, NJ; Schering; January 2015.
- 103 PEG-Intron [package insert]. Whitehouse Station, NJ; Schering; January 2015.
- 104 Sovaldi [package insert]. Foster City, CA; Gilead Sciences, Inc.; November 2014.
- 105 Olysio [package insert]. Titusville, NJ; Janssen Therapeutics; November 2014.
- 106 Sovaldi [package insert]. Foster City, CA; Gilead Sciences, Inc.; November 2014.
- 107 Harvoni [package insert]. Foster City, CA; Gilead Sciences, Inc.; October 2014.
- 108 Harvoni [package insert]. Foster City, CA; Gilead Sciences, Inc.; October 2014.
- 109 Harvoni [package insert]. Foster City, CA; Gilead Sciences, Inc.; October 2014.
- 110 Viekira Pak [package insert]. North Chicago, IL; AbbVie Inc.; January 2015.
- 111 Viekira Pak [package insert]. North Chicago, IL; AbbVie Inc.; January 2015.
- 112 Olysio [package insert]. Titusville, NJ; Janssen Therapeutics; November 2014.
- 113 McHutchison JG, Manns M, Patel K, et al for the International Hepatitis Interventional Therapy Group. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterol.* 2002; 123(4):1061-1069.
- 114 Jonas MM. Children with hepatitis C. *Hepatology.* 2002; 36(suppl 1):S173-S178.
- 115 Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, Management, and Treatment of Hepatitis C: An Update. *Hepatology.* 2009; April:1335-1374.
- 116 Bortolotti F, Resti M, Giacchino R, et al. Changing epidemiologic pattern of chronic hepatitis C virus infection in Italian children. *J Pediatr.* 1998; 133:378-381.
- 117 An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guideline by the American Association for the Study of Liver Diseases Available at: <http://www.aasld.org/practiceguidelines/Documents/AASLDUpdateTreatmentGenotype1HCV11113.pdf>. Accessed January 30, 2015.
- 118 PEG-Intron [package insert]. Whitehouse Station, NJ; Schering; January 2015.
- 119 Jara P, Hierro L, de la Vega A, et al. Efficacy and safety of peginterferon-alpha2b and ribavirin combination therapy in children with chronic hepatitis C infection. *Pediatr Infect Dis J.* 2008; 27(2):142-8.
- 120 Schwarz KB, Gonzalez-Peralta RP, Murray KF, et al. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. *Gastroenterology* 2011; 140:450-458.
- 121 Schwarz KB, Mohan P, Narkewicz MR, et al. Safety, efficacy and pharmacokinetics of peginterferon alpha2a (40 kd) in children with chronic hepatitis C. *J Pediatr Gastroenterol Nutr.* 2006; 43(4):499-505.
- 122 PEG-Intron [package insert]. Kenilworth, NJ; Schering; January 2015.
- 123 PEG-Intron [package insert]. Kenilworth, NJ; Schering; January 2015.
- 124 PEGASYS [package insert]. South San Francisco, CA; Genentech Inc.; September 2014.
- 125 Infergen [package insert]. Warrendale, PA; Three Rivers Pharmaceutical; July 2010.
- 126 Rebetol [package insert]. Whitehouse Station, NJ; Schering; December 2014.
- 127 Victrelis [package insert]. Whitehouse Station, NJ; Merck & Co; July 2014.
- 128 Incivek [package insert]. Cambridge, MA; Vertex Pharmaceuticals Incorporated; December 2012.
- 129 Olysio [package insert]. Titusville, NJ; Janssen Therapeutics; November 2014.
- 130 Sovaldi [package insert]. Foster City, CA; Gilead Sciences, Inc.; November 2014.
- 131 Harvoni [package insert]. Foster City, CA; Gilead Sciences, Inc.; October 2014.
- 132 Viekira Pak [package insert]. North Chicago, IL; AbbVie Inc.; January 2015.
- 133 Rebetol [package insert]. Whitehouse Station, NJ; Schering; December 2014.
- 134 Ribasphere [package insert]. Cranberry Twp, PA; Three Rivers Pharmaceuticals, 2005.
- 135 COPEGUS [package insert]. Nutley, NJ; Roche Pharmaceuticals; August 2011.
- 136 Ribapak [package insert]. Warrendale, PA; Kadmon Pharmaceutical; December 2014.
- 137 Victrelis [package insert]. Whitehouse Station, NJ; Merck & Co; July 2014.
- 138 Incivek [package insert]. Cambridge, MA; Vertex Pharmaceuticals Incorporated; December 2012.
- 139 Olysio [package insert]. Titusville, NJ; Janssen Therapeutics; November 2014.
- 140 Moderiba [package insert]. North Chicago, IL; AbbVie, Inc; January 2014.
- 141 Harvoni [package insert]. Foster City, CA; Gilead Sciences, Inc.; October 2014.
- 142 Viekira Pak [package insert]. North Chicago, IL; AbbVie Inc.; January 2015.
- 143 Muir AJ, Bornstein JD, Killenberg PG for the Atlantic Coast Hepatitis Treatment Group. Peginterferon Alfa-2b and Ribavirin for the Treatment of Chronic Hepatitis C in Blacks and Non-Hispanic Whites. *N Engl J Med.* 2004; 350:2265-71.
- 144 Conjeevaram HS, Fried MW, Jeffers LJ, et al for the Virahep-C Study Group. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology.* 2006; 131(2):470-7.
- 145 Rodriguez-Torres M, et al. Peginterferon Alfa-2a and Ribavirin in Latino and Non-Latino Whites with Hepatitis C. *N Engl J Med.* 2009; 360(3):257-267.
- 146 Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, Management, and Treatment of Hepatitis C: An Update. *Hepatology.* 2009; April:1335-1374.
- 147 Olysio [package insert]. Titusville NJ; Janssen Therapeutics; November 2014.
- 148 American Association for the Study of Liver Diseases/Infectious Diseases Society of America Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-hivhcv-coinfection>. Accessed February 9, 2015.
- 149 Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med.* 2011; 364(13):1207-1217.
- 150 Zeuzem S, Andreone P, Stanislas P, et al for the REALIZE Study Team. Telaprevir (Incivek) for Retreatment of HCV Infection. *N Engl J Med.* 2011; 364:2417-2428.

- 151 Victrelis [package insert]. Whitehouse Station, NJ; Merck & Co; July 2014.
- 152 American Association for the Study of Liver Diseases/Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C. Available at: <http://www.hcvguidelines.org/full-report/retreatment-persons-whom-prior-therapy-has-failed>. Accessed January 30, 2015.
- 153 Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, Management, and Treatment of Hepatitis C: An Update. *Hepatology*. 2009; April:1335-1374.
- 154 Olysio [package insert]. Titusville NJ; Janssen Therapeutics; November 2014.
- 155 Sovaldi [package insert]. Foster City, CA; Gilead Sciences, Inc.; November 2014.
- 156 American Association for the Study of Liver Diseases/Infectious Diseases Society of America Recommendations for Testing, Managing and Treating Hepatitis C Available at: <http://www.hcvguidelines.org/full-report/unique-patient-populations-renal-impairment-box-summary-recommendations-patients-renal>. Accessed January 30, 2015.
- 157 American Association for the Study of Liver Diseases/Infectious Diseases Society of America Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-renal-impairment>. Accessed January 30, 2015.
- 158 PEGASYS [package insert]. South San Francisco, CA; Genentech Inc.; September 2014.
- 159 COPEGUS [package insert]. Nutley, NJ; Roche Pharmaceuticals; February 2013.
- 160 Rebetal [package insert]. Whitehouse Station, NJ; Schering; December 2014.
- 161 Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, Management, and Treatment of Hepatitis C: An Update. *Hepatology*. 2009; April:1335-1374.
- 162 Olysio [package insert]. Titusville NJ; Janssen Therapeutics; November 2014.
- 163 Sovaldi [package insert]. Foster City, CA; Gilead Sciences, Inc.; November 2014.
- 164 American Association for the Study of Liver Diseases/Infectious Diseases Society of America Recommendations for Testing, Managing and Treating Hepatitis C Available at: <http://hcvguidelines.org/full-report/unique-patient-populations-patients-decompensated-cirrhosis>. Accessed January 26, 2015.
- 165 Olysio [package insert]. Titusville NJ; Janssen Therapeutics; November 2014.
- 166 Sovaldi [package insert]. Foster City, CA; Gilead Sciences, Inc.; November 2014.
- 167 American Association for the Study of Liver Diseases/Infectious Diseases Society of America Recommendations for Testing, Managing and Treating Hepatitis C. Available at: <http://hcvguidelines.org/full-report/unique-patient-populations-patients-who-develop-recurrent-hcv-infection-post%E2%80%93liver>. Accessed January 26, 2015.
- 168 Infergen [package insert]. Warrendale, PA; Three Rivers Pharmaceutical; July 2010.
- 169 COPEGUS [package insert]. Nutley, NJ; Roche Pharmaceuticals; February 2013.
- 170 PEG-Intron [package insert]. Whitehouse Station, NJ; Schering; January 2015.
- 171 Victrelis [package insert]. Whitehouse Station, NJ; Merck & Co; July 2014.
- 172 Incivek [package insert]. Cambridge, MA; Vertex Pharmaceuticals Incorporated; October 2013.
- 173 Sovaldi [package insert]. Foster City, CA; Gilead Sciences, Inc.; November 2014.
- 174 Olysio [package insert]. Titusville NJ; Janssen Therapeutics; November 2014.
- 175 Harvoni [package insert]. Foster City, CA; Gilead Sciences, Inc.; October 2014.
- 176 Viekira Pak [package insert]. North Chicago, IL; AbbVie Inc.; January 2015.
- 177 Sovaldi [package insert]. Foster City, CA; Gilead Sciences, Inc.; November 2014.
- 178 Olysio [package insert]. Titusville NJ; Janssen Therapeutics; November 2014.
- 179 Sporea I, Danila M, Sirli R, et al. Comparative study concerning the efficacy of Peg-IFN alpha-2a versus Peg-IFN alpha-2b on the early virological response (EVR) in patients with chronic viral C hepatitis. *J Gastrointest Liver Dis*. 2006; 15(2):125-30.
- 180 Di Bisceglie AM, Ghalib RH, Hamzeh FM, et al. Early virologic response after peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin treatment in patients with chronic hepatitis C. *J Viral Hepat*. 2007; 14(10):721-9.
- 181 Escudero A, Rodriguez F, Serra MA, et al. Pegylated alpha-interferon-2a plus ribavirin compared with pegylated alpha-interferon-2b plus ribavirin for initial treatment of chronic hepatitis C virus: prospective, non-randomized study. *J Gastroenterol Hepatol*. 2008; 23(6):861-6.
- 182 IDEAL final results presented at EASL. 43rd Annual Meeting of the European Association For The Study Of The Liver. Milan, Italy. April 23-27, 2008. Available at: http://www.natap.org/2008/EASL/EASL_17.htm. Accessed January 30, 2015.
- 183 McHutchison JG, Lawitz EJ, Shiffman ML, et al for the IDEAL Study Team. Peginterferon Alfa-2b or Alfa-2a with ribavirin for the Treatment of Hepatitis C Infection. *N Engl J Med*. 2009; 361:580-93.
- 184 Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs. peginterferon-alpha2b plus ribavirin in chronic hepatitis C. *Gastroenterology*. 2010; 138(1):108-15.
- 185 Ascione A, De Luco M, Tartaglione MT, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. *Gastroenterology*. 2010; 38(1):116-22.
- 186 Kamal SM, Ahmed A, Mahmoud S, et al. Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. *Liver Int*. 2011; 31(3):41-11.
- 187 Laguno M, Cifuentes C, Murillas J, et al. Randomized trial comparing pegylated interferon alpha-2b versus pegylated interferon alpha-2a, both plus ribavirin, to treat chronic hepatitis C in human immunodeficiency virus patients. *Hepatology*. 2009; 49(1):22-31.
- 188 Pockros PJ. The safety and tolerability of daily Infergen plus ribavirin in the treatment of naïve chronic hepatitis C patients. *J Viral Hepat*. 2003; 10:55-60.
- 189 Poordad F, McCone J, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011; 364(13):1195-1206.
- 190 Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011; 364(13):1207-1217.
- 191 Birnkrant, D. Director, Division of Antiviral Products, FDA. Advisory Committee Briefing Document for NDA 201-017 Telaprevir (Incivek) 375 mg tablets. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252561.pdf>. Accessed January 30, 2015.
- 192 Jacobson IR, McHutchison JG, Dusheiko G, et al for the ADVANCE Study Team. Telaprevir (Incivek) for Previously Untreated Chronic Hepatitis C Virus Infection. *N Engl J Med*. 2011; 364:2405-2416.
- 193 Zeuzem S, Andreone P, Stanislas P, et al for the REALIZE Study Team. Telaprevir (Incivek) for Retreatment of HCV Infection. *N Engl J Med*. 2011; 364:2417-2428.

- 194 Olysio [package insert]. Titusville, NJ; Janssen Therapeutics; November 2014.
- 195 Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir (Sovaldi) for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013; 368:1878-87. doi: 10.1056/NEJMoa1214853. Available at: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1214853>. Accessed January 30, 2015.
- 196 Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir (Sovaldi) for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013;368:1867-77. doi: 10.1056/NEJMoa1214854. Available at: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1214854>. Accessed January 30, 2015.
- 197 Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir (Sovaldi) for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013;368:1867-77. doi: 10.1056/NEJMoa1214854. Available at: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1214854>. Accessed January 30, 2015.
- 198 Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir (Sovaldi) for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013; 368:1878-87. doi: 10.1056/NEJMoa1214853. Available at: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1214853>. Accessed January 30, 2015.
- 199 FDA Antiviral Drugs Advisory Committee Meeting, October 25, 2013; Background Package for NDA 204671 Sofosbuvir (Sovaldi) (GS-7977).
- 200 Sovaldi [package insert]. Foster City, CA; Gilead, December 2013.
- 201 Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection. *N Engl J Med* 2014; 370: 1889-98 DOI: 10.1056/NEJMoa1402454.
- 202 Afdhal N, Reddy R, Nelson DR, et al. Ledipasvir and Sofosbuvir for Previously Treated HCV Genotype 1 Infection *N Engl J Med* 2014; 370:1483-93 DOI: 10.1056/NEJMoa1316366.
- 203 Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis *N Engl J Med* 2014; 370: 1879-88 DOI: 10.1056/NEJMoa1402355.
- 204 Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin *New Engl J Med* 2014 370:1594-603 DOI: 10.1056/NEJMoa1315722.
- 205 Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin *New Engl J Med* 2014; 370: 1604-14 DOI: 10.1056/NEJMoa1401561.
- 206 Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, Ritonavir, Ombitasvir and Dasabuvir Achieves 97% and 100% Sustained Virologic Response With or Without Ribavirin in Treatment Experienced Patients with HCV Genotype 1b Infection *Gastroenterology* 2014; 147:359-365 DOI: 10.1053/j.gastro.2014.04.045.
- 207 Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-Ombitasvir and Dasabuvir with or without Ribavirin for HCV *New Engl J Med* 2014; 370:1983-92 DOI: 10.1056/NEJMoa1402338.
- 208 Poordad F, Hezode C, Trinh R, et al. ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis *New Engl J Med* 2014; 370: 1973-82. DOI: 10.1056/NEJMoa1402869.
- 209 Viekira Pak [package insert]. North Chicago, IL; AbbVie Inc.; January 2015.
- 210 Kwo PY, Mantry PS, Coakley E, et al. An Interferon-free Antiviral Regimen for HCV after Liver Transplantation *New Engl J Med* 2014; 371:2375-82 DOI: 10.1056/NEJMoa1408921.
- 211 Chou R, Carson S, Chan BKS. Pegylated interferons for chronic hepatitis C virus infection: an indirect analysis of randomized trials. *Journal of Viral Hepatitis*. 2008; 15(8):578-590.
- 212 Awad T, Thorlund K, Hauser G, et al. Peginterferon alpha-2a is associated with higher sustained virological response than peginterferon alfa-2b in chronic hepatitis C: systematic review of randomized trials. *Hepatology*. 2010; 51(4):1176-84.
- 213 Chou R, Hartung D, Rahman B, et al. Comparative effectiveness of antiviral treatment of hepatitis C virus infection in adults: A systematic review. *Ann Intern Med* 2013;158:114-123.