Therapeutic Class Overview
Direct Acting Hepatitis C Antivirals and Combinations

Overview/Summary:
The direct acting hepatitis C antiviral and combination products are all Food and Drug Administration (FDA)-approved for the treatment of chronic hepatitis C virus (HCV) infection; although, differences in indications exist relating to use in specific genotypes, with certain combination therapies and other patient factors.[1-5] HCV is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood and is the most common bloodborne infection in the United States, with an estimated prevalence of 3.2 million people chronically infected. Chronic HCV develops in 70 to 85% of HCV-infected persons and is associated with significant morbidity (e.g., cirrhosis, hepatocellular carcinoma [HCC]) and is the leading cause of liver transplantation.[7,8] The average annual incidence rate of HCC in the U.S. between 2001 and 2006 was 3.0 per 100,000 people, with 48% to cases attributed to HCV.[9] These agents act via several different mechanisms of action and include inhibition of non-structural (NS) 3/4A protease, NS5B polymerase and HCV NS5A.[1-6] The hepatitis C protease inhibitors boceprevir (Victrelis®) and simeprevir (Olysio®) both work via inhibition of the HCV NS3/4A protease of HCV genotype 1a and 1b thus preventing replication of HCV host cells.[1-2] Similarly, sofosbuvir (Sovaldi®) inhibits HCV NS5B polymerase which also prevents the replication of HCV host cells, however, it is active against multiple genotypes of HCV.[3] The two combination products that include direct acting hepatitis C antivirals include ledipasvir/sofosbuvir (Harvoni®) and a 4-drug regimen of ombitasvir/paritaprevir/ritonavir & dasabuvir (Viekira Pak®). Paritaprevir and dasabuvir exert their mechanisms of action in the same was as other agents and inhibit NS3/4A protease and NS5B polymerase, respectively. Ledipasvir and Ombitasvir work along the same line as the other agents, but specifically inhibit HCV non-structural protein NS5A. Ritonavir, when used in Viekira Pak®, is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir along with overall drug exposure; it has no direct effect on the hepatitis C virus.[4-5] Specific indications for each of the direct acting hepatitis C antiviral agents are listed in Table 1.

Safety and efficacy of the direct acting hepatitis C agents have been established in multiple clinical trials.[10-25] Newly published guidelines developed by the American Association for the Study of Liver Diseases, Infectious Diseases Society of America and International Antiviral Society-USA have included all current treatments in their recommendations.[26] There are currently no generic direct acting hepatitis C agent available generically.

Table 1. Current Medications Available in Therapeutic Class[1-6]

Generic (Trade Name)	FDA Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Boceprevir (Victrelis®)	Treatment of chronic hepatitis genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders and relapsers	Capsule: 200 mg	-
Simeprevir (Olysio®)	Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin or in combination with sofosbuvir*	Capsule: 150 mg	-
Sofosbuvir (Sovaldi®)	Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin or ribavirin alone; treatment of	Tablet: 400 mg	-

Generic (Trade Name)	FDA Approved Indications	Dosage Form/Strength	Generic Availability
	chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin; prevention of post-transplant HCV reinfection in combination with ribavirin in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection		
Combination Products			
Ledipasvir/sofosbuvir (Harvoni®)	Treatment of chronic HCV genotype 1 infection in adults	Tablet: 90/400 mg	-
Ombitasvir/paritaprevir /ritonavir & dasabuvir (Viekira Pak®)	Treatment of chronic HCV genotype 1 infection in adults	Tablet (dasabuvir): 250 mg Tablet (ombitasvir/ paritaprevir/ ritonavir): 12.5/75/50 mg	-

FDA=Food and drug administration, HCV=hepatitis C virus, HIV=human immunodeficiency virus
*Although simeprevir is FDA-approved for combination therapy with sofosbuvir, the indication is only included on the FDA-approved label of simeprevir and is not listed in sofosbuvir's label.

Evidence-based Medicine

- The efficacy of boceprevir (Victrelis®) was assessed in two phase III clinical trials compromising approximately 1,500 adult patients.[1,13,18]
  - SPRINT-2 evaluated treatment-naïve patients. Sustained virologic response (SVR) was significantly higher in the response-guided therapy arm compared with placebo for both the black and non-black cohorts (P=0.04 and P<0.01). RESPOND-2 evaluated patients previously treated with peginterferon alfa and ribavirin, but who were not considered null responders. SVR was significantly improved in the response-guided therapy arm compared with placebo (P<0.001).[13]
  - An additional study, Flamm et al, evaluated the efficacy of boceprevir in combination with peginterferon alfa and ribavirin in patients who were relapsers or nonresponders to prior therapy. Overall SVR rates were 21 and 64% for control and the boceprevir-containing regimen respectively (P<0.001).[19]
- The efficacy of simeprevir (Olysio®) in patients with HCV genotype 1 infection was evaluated in several unpublished studies, including two phase III trials in treatment-naïve patients (QUEST 1 and QUEST 2), one phase III trial in patients who relapsed after prior interferon-based therapy (PROMISE).[2]
  - In the pooled analysis of QUEST 1 and QUEST 2, a greater proportion of patients in the simeprevir group achieved SVR at 12 weeks (SVR12) compared to control group (80 vs 50%; P value not reported).[2]
- The safety and efficacy of simeprevir in combination with sofosbuvir with or without ribavirin for the treatment of hepatitis C genotype 1 was evaluated in the COSMOS trial. Cohort 1 included prior null responders with METAVIR scores F0 to F2 and Cohort 2 included prior null responders and treatment-naïve patients with METAVIR scores F3 to F4.[2,20]
  - SVR at 12 weeks post therapy (SVR12) was achieved in 92% of the patients in the the intention to treat (ITT) population. SSVR12 for Cohort 1 and Cohort 2 were 90% (95% CI, 81

to 96) and 94% (95% CI, 87 to 98), respectively. The results were not significantly altered by use of ribavirin, duration of treatment, or treatment history (no P values reported). [20]

- The FDA approval of sofosbuvir was based on the results of five phase III trials (N=1,724) in HCV mono-infected patients (genotypes 1 to 6) and one unpublished phase III trial (N=223) in HCV/HIV-1 co-infected patients (HCV genotype 1, 2 or 3).[3,10,24,25]
  - All trials utilized SVR12 as the primary endpoint and overall, these studies showed that sofosbuvir provided a significant improvement in SVR12 compared with control in both treatment-naïve and treatment-experienced patients.[10,24,25]
  - Sofosbuvir was not specifically studied in treatment-experienced patients with HCV genotype 1 infection. According to the prescribing information, the estimated response rate in patient who previously failed treatment with peginterferon alfa and ribavirin is 71%. This is based on the observed response rate in patients from the NEUTRINO study.[3,10]
- The FDA approval of combination ledipasvir/sofosbuvir was based on the results of three phase III trials (N=1,518) in HCV mono-infected subjects with genotype 1 infection who had compensated liver disease. Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels.[4,11,12,17]
  - ION-1 evaluated treatment-naïve patients include patients with cirrhosis; ION-2 evaluated patients with or without cirrhosis who failed previous therapy with an interferon-based regimen including those containing an HCV protease inhibitor; ION-3 evaluated non-cirrhotic, treatment-naïve patients.[11,12,17]
  - All studies showed that ledipasvir/sofosbuvir significantly improved SVR12 rate compared to control.[11,12,17]
- The FDA approval of ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak®) was based on the results of six randomized, multicenter, clinical trials (N=2,308) in HCV patients with genotype 1, including one trial exclusively in patients with cirrhosis and mild hepatic impairment (Child-Pugh A). All studies included at least one treatment arm with ribavirin, while several studies included treatment arms without ribavirin.[5,14-16,21,22]
  - Study populations for each of the studies include treatment-naïve, non-cirrhotic adults with HCV genotype 1 infection (SAPPHIRE-I), treatment-naïve, non-cirrhotic adults with HCV genotype 1b and HCV genotype 1a infections (PEARL-III and PEARL-IV, respectively), treatment-naïve or previously treated with peginterferon alfa and ribavirin cirrhotic adults with HCV genotype 1 infection (TURQUOISE-II), noncirrhotic adults with HCV genotype 1 infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (SAPPHIRE-II) and finally, non-cirrhotic adults with HCV genotype 1b infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (PEARL-II).[14-16,21,22]
  - Overall, SVR12 rates were high and significantly improved compared with control after 12 weeks of thearpy.[14-16,21,22] Only TURQUOISE-II evaluated patients beyond 12 weeks of therapy and found there was no difference between 12 weeks of therapy compared with 24 weeks of therapy (P=0.09).[16]

Key Points within the Medication Class

- According to current clinical guidelines published by the American Association for the Study of Liver Diseases, Infectious Diseases Society of America and the International Antiviral Society-USA have been updated to include all currently available treatments with specific recommendations based on genotype, previous treatment history and special populations.[26]
- Old standards of therapy, including pegylated interferon alfa and ribavirin dual therapy and pegylated interferon alfa, ribavirin along with a protease inhibitor triple therapy are no longer recommended.
- Current, first-line therapies recommended in the new guidelines include all-oral combination therapies, each of which generally has at least one polymerase inhibitor and one other direct-acting agent that acts via a different mechanism of action.
- Depending on genotype, previous treatment-experience and special populations, the recommended regimens and durations of treatment vary due to differences in efficacy provided by clinical trials.
  - For genotype 1, three regimens with similar efficacy are recommended. Duration and addition of ribavirin depend on cirrhosis status and/or previous treatment failures.
    - § Ledipasvir/sofosbuvir 90/400 mg daily (QD) ± ribavirin for 12 to 24 weeks

        - § Paritaprevir/ritonavir/ombitasvir 150/100/25 mg QD + dasabuvir 250 mg twice-daily (BID) ± ribavirin for 12 to 24 weeks
        - § Sofosbuvir 400 mg QD + simeprevir 150 mg QD ± ribavirin for 12 to 24 weeks
    - o For genotype 2, the only 1st line regimen recommended is sofosbuvir 400 mg QD + ribavirin for 12 weeks (16 weeks with cirrhosis), regardless of previous treatment experience
    - o For genotype 3, the only 1st line regimen recommended is sofosbuvir 400 mg QD + ribavirin for 24 weeks
    - o For Genotype 4, three regimens are recommended, two of which are recommended independent of cirrhosis status and treatment experience and one of which is based on previous treatment failure.
        - § Ledipasvir/sofosbuvir 90/400 mg QD for 12 weeks
        - § Paritaprevir/ritonavir/ombitasvir 150/100/25 QD + ribavirin for 12 weeks
        - § Sofosbuvir 400 mg QD + ribavirin for 24 weeks (treatment-naïve) or sofosbuvir 400 mg QD + weight-based ribavirin for 24 weeks (previous treatment failure; may use for 12 weeks if pegylated interferon alfa added).
    - o In patients that fail a sofosbuvir-containing regimen, it is recommended to defer therapy unless the patient has advanced fibrosis; in this case, the only recommended regimen is ledipasvir/sofosbuvir 90/400 QD ± ribavirin for 24 weeks

- Other Key Facts:
    - o Prior to initiating therapy with simeprevir in combination with peginterferon and ribavirin, patients with HCV genotype 1a should be screened for the presence of NS3 Q80K polymorphism.[2]
        - § Screening for NS3 Q80K polymorphism is not necessary when used in combination with sofosbuvir that is associated with substantially reduced drug efficacy; alternative therapy should be considered if this polymorphism is present.[2]
    - o Sofosbuvir is a substrate of P-glycoprotein (P-gp). Thus, coadministration of potent P-gp inducers such as rifampin and St. John's wort should be avoided. Nevertheless, there are fewer drug interactions with sofosbuvir compared to the HCV protease inhibitors.[1,2,15-17]
    - o When prescribing ombitasvir/paritaprevir/ritonavir/dasabuvir, screening for drugs that should not be coadministered is recommended due to many, often severe, drug interactions.[5]

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Therapeutic Class Review
Direct Acting Hepatitis C Antivirals and Combinations

Overview/Summary

The direct acting hepatitis C antiviral and combination products are all Food and Drug Administration (FDA)-approved for the treatment of chronic hepatitis C virus (HCV) infection; although, differences in indications exist relating to use in specific genotypes, with certain combination therapies and other patient factors.[1-5]

HCV is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood and is the most common bloodborne infection in the United States, with an estimated prevalence of 3.2 million people chronically infected. Chronic HCV develops in 70 to 85% of HCV-infected persons and is associated with significant morbidity (e.g., cirrhosis, hepatocellular carcinoma [HCC]) and is the leading cause of liver transplantation.[7,8] The average annual incidence rate of HCC in the U.S. between 2001 and 2006 was 3.0 per 100,000 people, with 48% to cases attributed to HCV.[9] These agents act via several different mechanisms of action and include inhibition of non-structural (NS) 3/4A protease, NS5B polymerase and HCV NS5A.[1-6] The hepatitis C protease inhibitors boceprevir (Victrelis®) and simeprevir (Olysio®) both work via inhibition of the HCV NS3/4A protease of HCV genotype 1a and 1b thus preventing replication of HCV host cells.[1-2] Similarly, sofosbuvir (Sovaldi®) inhibits HCV NS5B polymerase which also prevents the replication of HCV host cells, however, it is active against multiple genotypes of HCV.[3] The two combination products that include direct acting hepatitis C antivirals include ledipasvir/sofosbuvir (Harvoni®) and a 4-drug regimen of ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®). Paritaprevir and dasabuvir exert their mechanisms of action in the same was as other agents and inhibit NS3/4A protease and NS5B polymerase, respectively. Ledipasvir and Ombitasvir work along the same line as the other agents, but specifically inhibit HCV non-structural protein NS5A. Ritonavir, when used in Viekira Pak®, is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir along with overall drug exposure; it has no direct effect on the hepatitis C virus.[4-5] Specific indications for each of the direct acting hepatitis C antiviral agents are listed in Table 2.

Efficacy of these agents have been established in multiple clinical trials.[10-25] Newly published guidelines developed by the American Association for the Study of Liver Diseases, Infectious Diseases Society of America and International Antiviral Society-USA have included all current treatments in their recommendations.[26] Generally speaking, combination regimens that include newer direct hepatis C antivirals are preferred over older pegylated interferon-based regimens (including those containing older protease inhibitors) due to a higher sustained virologic response (SVR) rate, improved side effects profile, and reduced pill burden. However, many different regimens with direct-acting agents or combinations, which may or may not also include ribavirin or pegylated interferon, are recommended based on HCV genotype, previous treatment experience and certain special populations. These regimens are summarized in Table 13. Currently, there are no generic direct-acting antivirals available.

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Products		
Boceprevir (Victrelis®)	NS3/4A protease inhibitor	-
Simeprevir (Olysio®)	NS3/4A protease inhibitor	-
Sofosbuvir (Sovaldi®)	NS5B polymerase inhibitor	-
Combination Products		
Ledipasvir/sofosbuvir (Harvoni®)	HCV NS5A inhibitor/ NS5B polymerase inhibitor	-
Ombitasvir/paritaprevir/ritonavir/ dasabuvir (Viekira Pak®)	HCV NS5A inhibitor/ NS3/4A protease inhibitor/ CYP3A4 inhibitor* & NS5B polymerase inhibitor	-

*Ritonavir is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir and overall drug exposure; it has no direct effect on hepatitis C virus

Indications

Table 2. Food and Drug Administration Approved Indications[1-6]

Indication	Boceprevir	Simeprevir	Sofosbuvir	Ledipasvir/ sofosbuvir	Ombitasvir/ paritaprevir /ritonavir /dasabuvir
Treatment of chronic HCV genotype 1 infection in adults				a	a
Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin		a	a		
Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with sofosbuvir		a *			
Treatment of chronic hepatitis genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders and relapsers	a				
Treatment of chronic HCV genotype 1 in combination with ribavirin alone (without peginterferon alfa)			a		
Treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin			a		
Treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin			a		
Prevention of post-transplant HCV reinfection in combination with ribavirin in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection			a		

HCV=hepatitis C virus, HIV=human immunodeficiency virus
*Although simeprevir is FDA-approved for combination therapy with sofosbuvir, the indication is only included on the FDA-approved label of simeprevir and is not listed in sofosbuvir's label.

Pharmacokinetics

Table 3. Pharmacokinetics[1-6]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Products				
Boceprevir	Not reported	9	None	3.4
Simeprevir	Not reported	<1	None	41
Sofosbuvir	Not reported	80	GS-461203	0.5
Combination Products				
Ledipasvir/ sofosbuvir	Not reported	<1/80	GS-461203 (sofosbuvir)	47
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Not reported	1.91 (ombitasvir)/ 8.8 (paritaprevir)/ 11.3 (ritonavir)/ 2 (dasabuvir)		21 to 25 (ombitasvir)/ 5.5 (paritaprevir)/ 4 (ritonavir)/ 5.5 to 6 (dasabuvir)

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the direct acting hepatitis C antivirals are outlined in Table 4.[10-25] Overall, data from clinical trials support the FDA-approved indications and dosing recommendations for these agents.

The efficacy of boceprevir (Victrelis®) was assessed in two phase III clinical trials compromising approximately 1,500 adult patients. The SPRINT-2 study evaluated boceprevir in previously untreated (treatment-naïve) patients, while the RESPOND-2 study evaluated patients who had failed previous peginterferon alfa and ribavirin but had demonstrated previous responsiveness to interferon based therapy (i.e., they were not null responders).[1] These studies were similar in design in that that patients co-infected with human immunodeficiency virus (HIV) or hepatitis B were excluded, there were three treatment regimens (control, response-guided therapy and fixed duration therapy) and all treatment regimens consisted of a four week lead-in period with standard therapy alone.[13,18] Patients were divided into two cohorts during SPRINT-2, non-black and black. Results regarding the primary efficacy endpoint of sustained virologic response (SVR) showed that response-guided and fixed duration therapies (i.e., boceprevir-containing regimens) were significantly higher among the nonblack and black cohorts, compared to control in treatment-naïve patients (SVR non-black cohort, 40, 67 and 68% for the control arm, response-guided therapy arm and fixed duration therapy arm; P<0.01 for both compared to placebo). Within the black cohort, the corresponding rates were 23, 42 and 53% (P=0.04 vs control for response-guided therapy and P=0.004 vs control for fixed duration therapy).[13] Unlike SPRINT-2, the RESPOND-2 study did not distinguish between non-black and black patients. SVR was again significantly higher with response-guided and fixed duration therapies (i.e., boceprevir-containing regimens) compared to control. Specifically, SVR rates were 21, 59 and 66% with control, response-guided therapy and fixed duration therapy, respectively (P<0.001 compared to control for both).[18] An additional study by Flamm et al evaluated the efficacy of boceprevir in combination with peginterferon alfa and ribavirin in patients who were relapsers or nonresponders to prior therapy. Overall SVR rates were 21 and 64% for control and the boceprevir-containing regimen respectively (P<0.001).[19]

The efficacy of simeprevir (Olysio®) in patients with HCV genotype 1 infection was evaluated in several unpublished studies, including two phase III trials in treatment-naïve patients (QUEST 1 and QUEST 2), one phase III trial in patients who relapsed after prior interferon-based therapy (PROMISE).[2] QUEST 1 and QUEST 2 were similarly designed, randomized, double-blind, placebo-controlled, two-arm, multicenter trials in which patients were treated with simeprevir for 12 weeks or placebo plus peginterferon afla-2a (QUEST 1 and 2) or peginterferon alfa-2b (QUEST 2) and ribavirin. In the pooled analysis of QUEST 1 and QUEST 2, a greater proportion of patients in the simeprevir group achieved SVR at 12 weeks (SVR12) compared to control group (80 vs 50%). In the simeprevir group, SVR12 rates were lower in patients with genotype 1a virus with the NS3 Q80K polymorphism at baseline (58%) compared to those without the Q80K polymorphism (84%). The corresponding SVR12 rates in the control group were 52 and 43%, respectively.[2] In PROMISE, a greater proportion of patients in the simeprevir group achieved SVR12 compared to control group (79 vs 37%). Again, patients with the genotype 1a virus with the NS3 Q80K polymorphism had lower SVR12 rates than those without it (47% compared to 78%, corresponding SVR12 rates in the control group were 30 and 26% respectively).[2]

The safety and efficacy of simeprevir in combination with sofosbuvir was evaluated in the COSMOS trial, a randomized, open-label, phase IIa trial evaluating a once daily combination of simeprevir 400 mg and sofosbuvir 150 mg with and without ribavirin for 12 and 24 weeks in HCV genotype 1 patients. The four-point score METAVIR scale was used to quantify the degree of inflammation and fibrosis of the liver. Cohort 1 included prior null responders with METAVIR scores F0 to F2 and Cohort 2 included prior null responders and treatment-naïve patients with METAVIR scores F3 to F4.[2,20] One hundred fifty-four (92%) of 167 of patients in the intention-to-treat (ITT) population achieved SVR12, 90% (95% CI, 81 to 96) in Cohort 1 and 94% (95% CI, 87 to 98) in Cohort 2. The results were not significantly altered by use of ribavirin, duration of treatment, or by use of previous treatment (P value not reported). No patients experienced on-treatment virological failure, including viral breakthrough. Six patients had viral relapse after the end of treatment. At the time of relapse, five of the six had developed resistance-associated mutations to simeprevir, but none to sofosbuvir.[20]

The FDA approval of sofosbuvir (Sovaldi®) was based on the results of five phase 3 trials (N=1,724) in HCV mono-infected patients (genotypes 1 to 6) and one unpublished phase 3 trial (N=223) in HCV/HIV-1 co-

infected patients (HCV genotype 1, 2 or 3). Sofosbuvir dose was 400 mg daily, ribavirin dose was weight-based at 1,000 to 1,200 mg daily in two divided doses when given with sofosbuvir, and the peginterferon alfa dose was 180 µg weekly. Treatment duration was fixed in each trial and was not guided by patients' HCV ribonucleic acid (RNA) levels. All trials utilized SVR12 as the primary endpoint and overall, these studies showed that sofosbuvir provided a significant improvement in SVR12 compared with control in both treatment-naïve and treatment-experienced patients.[10,24,25] However, sofosbuvir was not specifically studied in treatment-experienced patients with HCV genotype 1 infection. According to the prescribing information, the estimated response rate in patient who previously failed treatment with peginterferon alfa and ribavirin is 71%. This is based on the observed response rate in patients from the NEUTRINO study with multiple baseline factors associated with a lower response to interferon-based treatment (i.e., IL28B non-C/C alleles, HCV RNA >800,000 IU/mL and F3 to F4 fibrosis).[3,10,24,25]

The FDA approval of combination ledipasvir/sofosbuvir (Harvoni®) was based on the results of three phase III trials (N=1,518) in HCV mono-infected subjects with genotype 1 infection who had compensated liver disease. All three phase III trials evaluated efficacy of ledipasvir 90 mg/sofosbuvir 400 mg fixed-dose tablet administered once daily with or without ribavirin.[4] Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels. All trials were randomized, open-label studies that evaluated SVR12 as the primary endpoint.[11,12,17] The different populations studied include treatment-naïve patients include patients with cirrhosis (ION-1), patients with or without cirrhosis who failed previous therapy with an interferon-based regimen including those containing an HCV protease inhibitor (ION-2), and non-cirrhotic, treatment-naïve patients (ION-3). All studies showed that ledipasvir/sofosbuvir significantly improved SVR12 rate compared to control.[11,12,17]

The FDA approval of ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®) was based on the results of six randomized, multicenter, clinical trials (N=2,308) in HCV patients with genotype 1, including one trial exclusively in patients with cirrhosis and mild hepatic impairment (Child-Pugh A). These included the SAPPHIRE-I (double-blind), SAPPHIRE-II (double-blind), PEARL-II (open-label), PEARL-III (open-label), PEARL-IV (double-blind) and TURQUIOSE-II (open-label).[14-16,21,22] Each study used SVR12 as the primary endpoint and evaluated ombitasvir/paritaprevir/ritonavir once-daily added to dasabuvir twice-daily. All trials had a treatment arm that contained ribavirin added to ombitasvir/paritaprevir/ritonavir/dasabuvir, with the PEARL studies (II, III and IV) also having a treatment arm without ribavirin. Study populations for each of the studies include treatment-naïve, non-cirrhotic adults with HCV genotype 1 infection (SAPPHIRE-I), treatment-naïve, non-cirrhotic adults with HCV genotype 1b and HCV genotype 1a infections (PEARL-III and PEARL-IV, respectively), treatment-naïve or previously treated with peginterferon alfa and ribavirin cirrhotic adults with HCV genotype 1 infection (TURQUOISE-II), noncirrhotic adults with HCV genotype 1 infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (SAPPHIRE-II) and finally, non-cirrhotic adults with HCV genotype 1b infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (PEARL-II). Overall, SVR12 rates were high and significantly improved compared with control after 12 weeks of thearpy.[14-16,21,22] Only TURQUOISE-II evaluated patients beyond 12 weeks of therapy and found there was no difference between 12 weeks of therapy compared with 24 weeks of therapy (P=0.09).[16]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Genotype 1, 2, 3, 4, 5, and 6 Chronic Hepatitis: Treatment-Naïve Patients				
Lavitz et al[10] (NEUTRINO and FISSION) NEUTRINO: Sofosbuvir 400 mg once daily for 12 weeks and peginterferon alfa-2a 180 µg once weekly for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks FISSION: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs peginterferon alfa-2a 180 µg once weekly for 24 weeks and	NEUTRINO: MC, OL, SG Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 1, 4, 5, or 6), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV infection FISSION: AC, MC, OL, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV	NEUTRINO: N=327 12 weeks FISSION: N=499 24 weeks	NEUTRINO: Primary: SVR12 Secondary: Not reported FISSION: Primary: SVR12 Secondary: Not reported	NEUTRINO: Primary: Treatment with sofosbuvir added to peginterferon alfa-2a and ribavirin achieved a SVR12 in 90% of patients (95% CI, 87 to 93). In addition, this regimen was found to be more effective in achieving a SVR12 compared to an adjusted historical response rate of 60% (P<0.001) observed in studies of telaprevir and boceprevir. The rate of SVR12 was 92% (95% CI, 89 to 95) among patients without cirrhosis and 80% (95% CI, 67 to 89) among those with cirrhosis. A SVR12 occurred in 98% of patients with the CC genotype of IL28B, as compared to 87% of patients with the non–CC IL28B genotype. Rates of SVR12 were similar among various HCV genotypes: 89% for patients with genotype 1 (92% for genotype 1a and 82% for genotype 1b) and 96% for those with genotype 4. The single patients with genotype 5 and all six patients with genotype 6 achieved SVR12. Secondary: Not reported FISSION: Primary: A SVR12 was achieved in 67% of patients in both sofosbuvir plus ribavirin group and peginterferon alfa-2a plus ribavirin group. Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (56 vs 97%). Among patients with cirrhosis at baseline, 47% of patients receiving sofosbuvir plus ribavirin had a SVR12 compared to 38% of those receiving peginterferon alfa-2a plus ribavirin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ribavirin 800 mg/day in two divided doses for 24 weeks	infection			Secondary: Not reported
Afdhal et al[11] (ION 1) Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24	MC, OL, R Patients ≥18 years of age with chronic HCV genotype 1 infection who had not previously received treatment for HCV infection	N=865 12 to 24 weeks	Primary: SVR12 Secondary: Not reported	Primary: The SVR12 rates in all four treatment groups were higher than the historical rate of 60% (P<0.001 for all comparisons). The SVR rates were 99% (95% CI, 96 to 100) in the group that received 12 weeks of ledipasvir/sofosbuvir; 97% (95% CI, 94 to 99) in the group that received 12 weeks of ledipasvir/sofosbuvir with ribavirin; 98% (95% CI, 95 to 99) in the group that received 24 weeks of ledipasvir/sofosbuvir; and 99% (95% CI, 97 to 100) in the group that received 24 weeks of ledipasvir/ sofosbuvir with ribavirin. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks				
Kowdley et al[12] (ION 3) Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 8 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 8 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks	MC, OL, R Patients ≥18 years of age with chronic HCV genotype 1 infection without cirrhosis who had not previously received treatment for HCV infection	N=647 8 to 12 weeks	Primary: SVR12 Secondary: Noninferiority of eight weeks of ledipasvir/ sofosbuvir to the other treatment regimens	Primary: The SVR12 rates in all four treatment groups were higher than the historical rate of 60% (P<0.001 for all comparisons). The SVR12 rate was 94% (95% CI, 90 to 97) with eight weeks of ledipasvir/sofosbuvir, 93% (95% CI, 89 to 96) with eight weeks of ledipasvir/sofosbuvir with ribavirin, and 95% (95% CI, 92 to 98) with 12 weeks of ledipasvir/sofosbuvir. Secondary: Treatment with ledipasvir/sofosbuvir for eight weeks was noninferior to both the 8-week ledipasvir/sofosbuvir + ribavirin treatment arm (treatment difference 0.9%; 95% CI, -3.9 to 5.7%) and the 12-week ledipasvir/sofosbuvir treatment arm (treatment difference -1.4%; 95% CI, -6.4 to 3.6%).
Poordad et al[13] SPRINT-2 Group 1 (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group 2 (response-guided	PC, PG, RCT Patients ≥18 years of age with a history of no previous treatment for HCV infection, weight 40 to 125 kg, chronic infection with HCV genotype 1 and	N=1,097 (N=938 [nonblack], N=159 [black]) 48 weeks (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Not reported	Primary: Among nonblack patients, the rate of SVR was 40, 67 and 68% in Groups 1, 2 and 3 (P<0.001 vs Group 1 for both Group 2 and 3). The corresponding numbers in black patients were 23, 42 (P=0.04 vs Group 1) and 53% (P=0.004 vs Group 1). Subgroup analyses revealed that at four weeks, 23 and 38% of nonblack and black patients had a decrease of <1 $\log_{10}$ IU/mL in HCV RNA level from baseline, which was associated with lower rates of SVR and higher rates of boceprevir-resistance-associated variants compared to those achieving a decrease of ≥1 $\log_{10}$ IU/mL from baseline. However, regardless of the degree of reduction achieved at week four, patients receiving boceprevir achieved consistently higher rates of SVR

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 24 weeks, followed by an additional 20 weeks of peginterferon alfa-2b plus ribavirin in detectable HCV RNA levels at any visit from week 8 to 24 vs Group 3 (fixed duration therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peginterferon alfa-2b and ribavirin were administered. The trial consisted of two cohorts enrolling nonblacks and blacks sepa4rately. Treatment was considered complete in Group 2 if the HCV RNA level was undetectable from week 8 through week 24 (total duration, 28 weeks). In all 3 treatment groups, treatment was discontinued for all	plasma HCV RNA level ≥10,000 IU/mL			compared to patients who received control overall. Adverse events occurred in more than 98% of all patients, with serious adverse events in 9, 11 and 12% of patients in Groups 1, 2 and 3, respectively. There were six deaths during the trial; four deaths in Group 1 and two deaths from boceprevir-containing regimens. Two suicides (one in Group 1 and one in Group 2) were determined to have possibly been related to treatment with peginterferon. Fatigue, headache and nausea were the most commonly reported adverse events. The incidence of dysgeusia was higher with boceprevir treatment. Anemia was reported in 29 and 49% of patients receiving control and boceprevir, respectively. Overall, 13 and 21% of control- and boceprevir-treated patients required dose reductions because of anemia and erythropoietin was administered in 24 and 43% of patients. Neutropenia and thrombocytopenia also occurred more frequently with boceprevir treatment. Secondary: Not reported Response rates at the end of therapy (undetectable HCV RNA level at the time that the study therapy was discontinued) were significantly higher with boceprevir-containing regimens compared to the control regimen. Among nonblack patients, viral breakthrough (undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) occurred in one to two percent of all patients, regardless of treatment regimen. In addition, relapse rates (undetectable HCV RNA level at the end of treatment but a detectable HCV RNA level at some point during the follow up period) were lower with boceprevir compared to control. The numbers of events among black patients were too few to permit comparison between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
patients with a detectable HCV RNA level at week 24 based on futility rules; these patients then entered the follow up period.				
Feld et al[14] (SAPPHIRE-I) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks (Group A) vs placebo for 12 weeks of double-blind period followed by active regimen as open-label therapy for 12 weeks (Group B)	DB, MC, PC, R Patients 18 to 70 years of age with chronic HCV genotype 1 infection, no cirrhosis, who had not previously received treatment for HCV infection, and HCV RNA> 10,000 IU/mL	N=631 12 weeks	Primary: SVR12 Secondary: Normalization of the alanine aminotransferase level, SVR12 by HCV subtype (1a or 1b), virologic failure during treatment, and posttreatment relapse	Primary: The SVR12 rate in group A (96.2%; 95% CI, 94.5 to 97.9) was statistically noninferior and superior to the calculated historical control rate of 78% (95% CI, 75 to 80) in treatment-naïve patients without cirrhosis who received telaprevir and PEG/RBV. Secondary: The SVR12 rate was 95.3% (95% CI, 93.0 to 97.6) among patients with HCV genotype 1a infection and 98.0% (95% CI, 95.8 to 100) among those with HCV genotype 1b infection. These rates were statistically superior to the historical control rates in the respective subgroups (72%; 95% CI, 68 to 75 in patients with HCV genotype 1a infection and 80%; 95% CI, 75 to 84 in those with HCV genotype 1b infection). The rate of normalization of the alanine aminotransferase level was 97.0% in group A as compared with 14.9% in group B (P<0.001). Virologic failure during treatment and relapse after treatment occurred in 0.2% and 1.5%, respectively, of the patients in group A.
Ferenci et al[15] (PEARL-III and PEARL-IV) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks	DB, MC, R Patients 18 to 70 years of age with chronic HCV genotype 1b infection (PEARL-	PEARL-III N=419 12 weeks PEARL-IV N=305	Primary: SVR12 Secondary: Superiority of the SVR12 rate at each	Primary: In the genotype 1a study, the SVR12 rates were 97.0% (95% CI, 93.7 to 100) in patients who received the regimen with ribavirin and 90.2% (95% CI, 86.2 to 94.3) in patients who received the regimen without ribavirin. In the genotype 1b study, the SVR12 rates were 99.5% (95% CI, 98.6 to 100.0) in patients who received the regimen with ribavirin and 99.0% (95%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and placebo	III) or HCV genotype 1a infection (PEARL-IV), no cirrhosis, who had not previously received treatment for HCV infection, and HCV RNA> 10,000 IU/mL	12 weeks	group as compared with the historical rate with telaprevir plus PEG/RBV, noninferiority of the SVR12 rate in the groups that did and did not receive ribavirin, hemoglobin level below the lower limit of the normal range at the end of treatment, and the percentage of patients in each group with virologic failure during treatment or relapse after treatment	CI, 97.7 to 100.0) in patients who received the regimen without ribavirin. Secondary: In the genotype 1a study, the SVR rates among patients who received ribavirin and those who did not were both noninferior and superior to the historical rate with telaprevir and PEG/RBV in treatment-naïve adults with HCV genotype 1a infection and no cirrhosis. The regimen without ribavirin did not meet the noninferiority criterion as compared with the regimen with ribavirin, because the lower boundary of the CI for the difference (-6.8%; 95% CI, -12.0 to -1.5) crossed the noninferiority margin of 10.5%. In addition, the upper boundary of the confidence interval did not cross zero, indicating a significant difference between groups. In the genotype 1b study, the SVR rates among patients who received ribavirin and those who did not were both noninferior and superior to the historical rate with telaprevir and PEG/RBV among previously untreated adults with HCV genotype 1b infection and no cirrhosis. In addition, the SVR rate among patients who did not receive ribavirin was noninferior to the rate among those who received ribavirin (difference, -0.5%; 95% CI, -2.1 to 1.1). Among the patients in the genotype 1a study who had a hemoglobin level within the normal range at baseline, 42.0% of patients who received the antiviral regimen with ribavirin and 3.9% of patients who received the ribavirin-free regimen had a hemoglobin level below the lower limit of the normal range at the end of treatment (P<0.001). Similarly, in the genotype 1b study, 51.2% of patients who received ribavirin had a low hemoglobin level at the end of treatment, as compared with 3.4% of patients who did not receive ribavirin (P<0.001). Among patients with genotype 1a infection, the rate of virologic failure was higher in the ribavirin-free group than in the group receiving ribavirin (7.8 vs 2.0%). Of patients with genotype 1b infection, none had virologic failure in the ribavirin-free group and one had virologic failure (0.48%) in the group receiving ribavirin.
Poordad et al[16] (TURQUOISE-II)	MC, OL, R	N=380	Primary: SVR12	Primary: The SVR12 rates were 91.8% (97.5% CI, 87.6 to 96.1) in the 12-week group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 24 weeks and dasabuvir 250 mg twice daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24 weeks	Patients 18 to 70 years of age with chronic HCV genotype 1 infection, treatment-naïve or previously treated with PEG/RBV, documented cirrhosis by means of liver biopsy, Child–Pugh class A score <7, no current or past clinical evidence of Child–Pugh class B or C, HCV RNA >10,000 IU/mL, platelets ≥60,000/mm^3, serum albumin ≥2.8 g/dL, total bilirubin <3 mg/dL, INR≤2.3, and serum alpha-fetoprotein ≤100 ng/mL	12 to 24 weeks	compared to historical control Secondary: SVR12 with 12- vs 24-week treatment, virologic failure during treatment or relapse after treatment	and 95.9% (97.5% CI, 92.6 to 99.3) in the 24-week group. These rates were statistically noninferior and superior to the historical control rate with telaprevir and PEG/RBV among patients with HCV genotype 1 infection and cirrhosis (47%; 95% CI, 41 to 54). Secondary: The difference in the SVR12 rates between the 12- and 24-week treatment groups was not significant (P=0.09). The SVR rates with 12- vs 24-week treatment were 88.6 vs 94.2% in genotype 1a patients; 98.5 vs 100% in genotype 1b patients; 94.2 vs 94.6% in treatment-naïve patients; 96.6 vs 100% in relapsers with prior PEG/RBV; 94.4 vs 100% in prior partial responders to PEG/RBV; and 86.7 vs 95.2% in prior null responders to PEG/RBV. Among patients with HCV genotype 1a infection and a prior null response to PEG/RBV, SVR was achieved in 92.9% (95% CI, 85.1 to 100) in the 24-week group as compared to 80.0% (95% CI, 68.9 to 91.1) in the 12-week group. Virologic failure during treatment or relapse after treatment occurred in 6.2% and 2.3% of patients in the 12-week and 24-week groups, respectively. Virologic failure during treatment occurred 0.5% (95% CI, 0 to 1.4) and 1.7% (95% CI, 0 to 3.7) of patients in the 12-week and 24-week groups, respectively. Significantly more patients in the 12-week group than in the 24-week group had a relapse: 5.9% (95% CI, 2.7 to 9.2) vs 0.6% (95% CI, 0 to 1.8).
Treatment of Genotype 1: Treatment-Experienced Patients				
Afdhal et al[17]	MC, OL, R	N=440	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(ION 2) Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24 weeks	Patients ≥18 years of age with chronic HCV genotype 1 infection who had not had a SVR with either PEG/ribavirin or NS3/4A protease inhibitor combined with PEG/ribavirin	12 to 24 weeks	SVR12 Secondary: SVR24	In all four treatment groups, the SVR12 rate was higher than the adjusted historical response rate of 25% (P<0.001 for all comparisons). The SVR12 rates was 94% (95% CI, 87 to 97) in the group that received 12 weeks of ledipasvir/sofosbuvir; 96% (95% CI, 91 to 99) in the group that received 12 weeks of ledipasvir/sofosbuvir with ribavirin; 99% (95% CI, 95 to 100) in the group that received 24 weeks of ledipasvir/sofosbuvir; and 99% (95% CI, 95 to 100) in the group that received 24 weeks of ledipasvir/sofosbuvir with ribavirin. Among patients with cirrhosis who were assigned to 12 weeks of treatment, the SVR12 rates were 86% for those who received ledipasvir/sofosbuvir and 82% for those who received ledipasvir/sofosbuvir with ribavirin; the respective rates among patients without cirrhosis were 95% and 100%. Among patients with cirrhosis who were assigned to 24 weeks of treatment, the SVR12 rates were 100% for those who received ledipasvir/sofosbuvir and 100% for those who received ledipasvir/sofosbuvir with ribavirin; the respective rates among patients without cirrhosis were 99% and 99%. The difference between the SVR rates among patients with cirrhosis who received 12 weeks of treatment and the SVR among patients with cirrhosis who received 24 weeks of treatment was statistically significant (P=0.007). Secondary: All patients who had a SVR12 also had a SVR24. No patient had a relapse after post-treatment week 12.
Bacon et al[18] RESPOND-2	PC, PG, RCT Patients with	N=403 48 weeks	Primary: SVR, safety	Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to control, with overall rates of SVR of 21, 59 and 66% in Groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Group 1 (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group 2 (response-guided therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 32 weeks, followed by an additional 12 weeks of peginterferon alfa-2b plus ribavirin in detectable HCV RNA levels at week 8 but undetectable at week 12 vs Group 3 (fixed duration therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peginterferon alfa-2b and ribavirin were administered. Treatment was considered complete in Group 2 if the HCV RNA level was undetectable at weeks 8 and 12 (total duration,	chronic HCV genotype 1 infection who demonstrated responsiveness to interferon (minimum duration of therapy, 12 weeks)	(plus 24 weeks of follow up)	Secondary: Proportion of patients with an early response in whom a SVR was achieved, proportion of patients with a relapse	1, 2 and 3, respectively (P<0.001). The increase observed with Groups 2 and 3 was largely due to end of treatment rates of response being higher (70 and 77 vs 31%) and relapse rates being lower (15 and 12 vs 32%) compared to Group 1. The absolute difference between Groups 2 and 1 was 34.7 percentage points (95% CI, 25.7 to 49.1), and between Groups 3 and 1 it was 45.2 percentage points (95% CI, 33.7 to 56.8). There was no difference in SVR rates between Groups 2 and 3 (OR, 1.4; 95% CI, 0.9 to 2.2). Overall, the most common adverse events were flulike symptoms, while dysgeusia, rash and dry skin were more commonly reported with boceprevir-containing regimens. A greater proportion of patients receiving boceprevir reported serious adverse events, and there were more discontinuations and dose modifications due to adverse events with boceprevir. Anemia occurred more frequently with boceprevir (43 to 46 vs 20%), and erythropoietin was administered more frequently to patients receiving boceprevir. Secondary: The proportion of patients with an undetectable HCV RNA level at week eight in Groups 2 and 3 (46 and 52%) was approximately six times the proportion in Group 1 (9%). Early response was associated with a high rate of SVR in all three treatment groups (100, 86 and 88% in Groups 1, 2 and 3; P values not reported). The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 29, 69 and 75% in Groups 1, 2 and 3; respectively (P values not reported). And the patients with prior nonresponse (a decrease in the HCV RNA level of ≥2 $\log_{10}$ IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR), the corresponding rates were 7, 40 and 52% (P values not reported). Virologic breakthrough (achievement of an undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) and incomplete virologic response (an increase of 1 $\log_{10}$ IU/mL in the HCV RNA level from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
36 weeks). In addition, in all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 12 based on futility rules; these patients then entered the follow up period.				the nadir, with an HCV RNA level >1,000 IU/mL) were infrequent during the treatment period. Multivariable stepwise logistic-regression analysis served to identify five baseline factor that were significantly associated with achievement of a SVR: assignment to boceprevir (OR for Groups 2 and 3 vs Group 1, 7.3 and 10.7, respectively; P<0.001 for both), previous relapse (OR vs previous nonresponse, 3.1; P<0.001), low viral load at baseline (OR vs high load, 2.5; P=0.02) and absence of cirrhosis (OR vs presence, 2.1; P=0.04).
Flamm et al[19] Peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day plus placebo for 48 weeks total vs boceprevir 800 mg three times a day plus peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 44 weeks (total treatment duration of 48 weeks) All patients entered a 4 week lead in period in which peginterferon alfa-2a and ribavirin were administered. In addition, in all treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 12 based on futility rules; these patients then entered the	PC, PG, RCT Patients with chronic HCV genotype 1 infection who were relapsers or nonresponders to a previous course of peginterferon alfa and ribavirin	N=201 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Proportion of patients whom a SVR was achieved by prior response (relapse and nonresponse), safety	Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to placebo, with overall rates of SVR of 21% in the peginterferon/ribavirin only treatment group compared to and SVR rate of 64% with boceprevir (P<0.001). Secondary: The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 28% in the peginterferon/ribavirin only treatment group compared to and SVR rate of 70% with boceprevir (P values not reported). The rates of SVR among patients with prior nonresponse (a decrease in the HCV RNA level of ≥2 $\log_{10}$ IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR), were 5% in the peginterferon/ribavirin only treatment group compared to and SVR rate of 47% with boceprevir (P values not reported). Overall, the most common adverse events were flulike symptoms, while dysgeusia, diarrhea, rash, myalgia, leukopenia and vomiting were more commonly reported with boceprevir-containing regimens. A greater proportion of patients receiving boceprevir reported serious adverse events (13 vs 10%), and there were more discontinuations (17 vs 3%) and dose modifications (43 vs 22%) due to adverse events with boceprevir.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
follow up period.				Anemia occurred more frequently with boceprevir (50 vs 57%). Anemia was managed with dose reduction in 8% of control group and 0% in the boceprevir group. Erythropoietin was administered more frequently to patients receiving boceprevir (28 vs 29%) and a combination of both interventions in 56% of the placebo group and 57% of the boceprevir group). Neutropenia occurred more frequently with boceprevir (31 vs 18%), and granulocyte colony-stimulating factor administered more frequently with boceprevir (14 vs 12%). Secondary: Not reported
Lawitz et al[20] COSMOS Cohort 1: Simeprevir 150 mg daily plus sofosbuvir 400 mg daily vs simeprevir 150 mg daily plus sofosbuvir 400 mg daily plus ribavirin 1,000 to 1,200 mg daily (based on body weight) Cohort 2: Simeprevir 150 mg daily plus sofosbuvir 400 mg daily vs simeprevir 150 mg daily plus sofosbuvir 400 mg daily	OL, MC, RCT Patients ≥18 years of age with a diagnosis of hepatitis C genotype 1, HCV RNA >10,000 IU/mL and HIV negative Cohort 1: Previous non-responders to peginterferon and ribavirin and no to moderate liver fibrosis Cohort 2: Previous non-responders to peginterferon and ribavirin or	N=167 Cohort 1 N=80 Cohort 2 N=87	Primary: SVR12 Secondary: SVR4, SVR24, rapid virological response, on-treatment failure and viral relapse	Primary: One hundred fifty-four (92%) of 167 of patients in the ITT population achieved SVR12, 90% (95% CI, 81 to 96) in Cohort 1 and 94% (95% CI, 87 to 98) in Cohort 2. The results were not significantly altered by use of ribavirin, duration of treatment, or by use of previous treatment (P value not reported). Secondary: All patients who achieved SVR12 also achieved SVR4. More than 91% of patients overall achieved SVR4. Rapid virological response was achieved in 81% of patients overall, but SVR12 was still achieved in all but one who had detectable HCV RNA titers four weeks after the start of treatment. No patients experienced on-treatment virological failure, including viral breakthrough. Six patients had viral relapse after the end of treatment. At the time of relapse, five of the six had developed resistance-associated mutations to simeprevir (Arg155Lys, Asp168Glu, Ile170Thr), but none to sofosbuvir. Five had received 12 weeks of treatment, and four had the HCV Gln80Lys polymorphism at baseline. Viral relapse was not associated with reduced speed of viral decay during weeks one to four of treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
plus ribavirin 1,000 to 1,200 mg daily (based on body weight)	treatment naïve and have severe liver fibrosis			
Zeuzem et al[21] (SAPPHIRE-II) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs placebo	MC, DB, PC, R Patients 18 to 70 years of age with chronic HCV genotype 1 infection without cirrhosis, relapsers or nonresponders with prior PEG/RBV treatment, and HCV RNA >10,000 IU/mL	N=394 12 weeks	Primary: SVR12 compared to historical control Secondary: Normalization of the alanine aminotransferase level, SVR by HCV genotype (1a or 1b), virologic failure during treatment, and post-treatment relapse	Primary: Treatment with the active-regimen lead to a SVR12 of 96.3% (95% CI, 94.2 to 98.4) which was noninferior and superior to the historical control SVR rate of 65% (95% CI, 60 to 70) among previously treated patients with HCV genotype 1 infection and no cirrhosis who had received retreatment with telaprevir and PEG/RBV (P value not reported). Secondary: The rate of normalization of the alanine aminotransferase level was significantly higher in the active-regimen group than in the placebo group (96.9 vs 12.8%, P<0.001). The SVR rates were similar between patients with HCV genotype 1a infection (96.0%; 95% CI, 93.0 to 98.9) and those with HCV genotype 1b infection (96.7%; 95% CI, 93.6 to 99.9). The HCV genotype (1a or 1b) could not be determined for one patient, who had a SVR12. No patient had virologic failure during treatment. Of the 293 patients who completed therapy, 2.4% had a post-treatment viral relapse.
Andreone et al[22] (PEARL-II) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for	MC, OL, R Patients 18 to 70 years of age with chronic HCV genotype 1b infection for at least six months, and HCV RNA >10,000 IU/mL, no cirrhosis,	N=179 12 weeks	Primary: SVR12 compared to historical control Secondary: Proportion of patients with decreased	Primary: The SVR12 rate was 96.6% (95% CI, 92.8 to 100) in the group receiving ribavirin and 100% (95% CI, 95.9 to 100) in the group not being treated with ribavirin. These rates were statistically noninferior to the historical SVR rate for telaprevir and PEG/RBV in comparable treatment-experienced patients. Secondary: Hemoglobin levels less than the lower limit of normal at the end of treatment were more common in patients receiving ribavirin compared to those that did not (42.0 vs 5.5%, respectively; P<0.001), although clinically significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks	and prior failure of therapy with PEG/RBV		hemoglobin level to less than the lower limit of normal at the end of treatment, superiority of both groups to historical SVR rate, noninferiority of both treatment groups, virologic failure during treatment, and post-treatment relapse	grade 2 hemoglobin level declines to <10 g/dL at the end of treatment occurred in only two patients (1.1%), both in the group receiving ribavirin. The SVR12 rates in the group receiving ribavirin (96.6%) and in the group not being treated with ribavirin (100%) were statistically superior to the historical SVR rate for telaprevir and PEG/RBV in comparable treatment-experienced patients. The SVR12 rates in the group not receiving ribavirin were noninferior to those in the group receiving ribavirin (difference, 3.4%; 95% CI, -0.4 to 7.2) No patients from either treatment group experienced on-treatment virologic failure or post-treatment relapse. Of the three patients in the group receiving ribavirin who did not achieve SVR12, there were two patients (2.3%) who discontinued study drug.
Treatment-naïve and -experienced subjects with HCV genotype 1 infection status post liver transplant				
Kwo et al[23] (CORAL-I) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 24 weeks and dasabuvir 250 mg twice daily for 24 weeks and ribavirin (dosing at investigator's discretion) for 24 weeks	MC, OL Patients 18 to 70 years of age with chronic HCV genotype 1 infection, HCV RNA >10,000 IU/mL who received a liver transplant ≥12 months before screening because of chronic HCV infection, and Metavir score≤F2	N=34 24 weeks	Primary: SVR12 Secondary: SVR24, virologic failure during treatment, and post-treatment relapse	Primary: The SVR12 rate was 97% (95% CI, 85 to 100). All five patients infected with genotype 1b (100%) and 28 of 29 patients infected with genotype 1a (97%) had a SVR. Secondary: The SVR24 rate was 97% (95% CI, 85 to 100). All the patients also had HCV RNA <25 IU/mL at the end of treatment. One patient did not have a SVR owing to a relapse on post-treatment day three. No relapses occurred after post-treatment week 12.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
A stable tacrolimus- or cyclosporine-based immunosuppressive regimen was required, and glucocorticoids were allowed at a dose of ≤5 mg/day.	on liver biopsy performed ≤6 months before screening			
Treatment of Genotype 2 and 3 Chronic Hepatitis: Treatment-Naïve and Experienced Patients				
Jacobson et al[24] (POSITRON and FUSION) POSITRON: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs placebo FUSION: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 12 weeks	POSITRON: DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who are not candidates for interferon therapy FUSION: AC, DB, MC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection	POSITRON: N=278 12 weeks FUSION: N=201 12 to 16 weeks	POSITRON: Primary: SVR12 Secondary: Not reported FUSION: Primary: SVR12 Secondary: Not reported	POSITRON: Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 78% of patients (95% CI, 72 to 83) compared to 0% among those receiving placebo (P<0.001). Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (61 vs 93%). Among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, 21% of patients with cirrhosis achieved a SVR12 compared to 68% without cirrhosis. Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, 94% of patients with cirrhosis achieved a SVR12 compared to 92% without cirrhosis. Secondary: Not reported FUSION: Primary: Treatment with sofosbuvir plus ribavirin resulted in higher rates of SVR12 in the 12-week group (50%; 95% CI, 40 to 60) and 16-week group (73%; 95% CI, 63 to 81) compared to historical control rate of 25%.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs sofosbuvir 400 mg once daily for 16 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 16 weeks	(genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who have previously not responded to treatment with an interferon containing regimen			Patients receiving 16 weeks of treatment had a significantly higher rate of SVR than patients receiving 12 weeks of treatment (difference, -23%; 95% CI, -35 to -11; P<0.001). Response rates in patients with genotype 2 infection who received 12 weeks of treatment were lower than among those who received 16 weeks of treatment (86 vs 94%; difference of -8%; 95% CI, -24 to 9); however, the difference was not statistically significant. Response rates in patients with genotype 3 infection who received 12 weeks of treatment were significantly lower than among those who received 16 weeks of treatment (difference, -32%; 95% CI, -48 to -15). Among patients with cirrhosis who received 12 weeks of treatment, the rate of response was 31% (60% with HCV genotype 2 infection and 19% with HCV genotype 3 infection), as compared to 61% among patients without cirrhosis (96% with HCV genotype 2 infection and 37% with HCV genotype 3 infection). Among patients with cirrhosis who received 16 weeks of treatment, the rate of response was 66% (78% with HCV genotype 2 infection and 61% with HCV genotype 3 infection) as compared to 76% among patients without cirrhosis (100% with HCV genotype 2 infection and 63% with HCV genotype 3 infection). Secondary: Not reported
Zeuzem et al[25] (VALENCE) Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight	DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3)	N=419 12 weeks (genotype 2) or 24 weeks (genotype 3)	Primary: SVR12 Secondary: Not reported	Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 93% (95% CI, 85 to 98) of patients with HCV genotype 2 receiving 12 weeks of therapy and 85% (95% CI, 80 to 89) of patients with HCV genotype 3 receiving 24 weeks of therapy. Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (96.7%; 95% CI, 82.8 to 99.9), treatment-naïve cirrhotics (100%; 95% CI, 15.8 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs placebo After study initiation, on the basis of emerging data from phase 3 trials, the study was unblinded, treatment for all patients with genotype 3 infection was extended to 24 weeks, the placebo group was terminated, and the goals of the study were redefined to be descriptive and not include hypothesis testing.	and serum HCV RNA levels of ≥10,000 IU/mL during screening			100), and treatment-experienced non-cirrhotics (93.8%; 95% CI, 79.2 to 99.2), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 2 infection (77.8%; 40.0 to 97.2). Similarly, among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (94.6%; 95% CI, 86.3 to 97.6), treatment-naïve cirrhotics (92.3%; 95% CI, 64.0 to 99.8), and treatment-experienced non-cirrhotics (86.7%; 95% CI, 78.4 to 92.7), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 3 infection (61.7%; 46.4 to 75.5). Secondary: Not reported

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel group, R=randomized, RCT=randomized control trial, SG=single-group
Miscellaneous abbreviations: HCV=hepatitis C virus, PEG=peginterferon, RBV=ribavirin, RNA=ribonucleic acid, SVR=sustained virologic response, SVR12=sustained virologic response at 12 weeks after post-therapy, SVR24= sustained virologic response at 24 weeks post-therapy

Special Populations

Table 5. Special Populations[1-6]

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Products					
Boceprevir	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	B*	Unknown; use with caution.
Simeprevir	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild impairment; safety and efficacy in moderate to severe hepatic impaired have not been established.	C*	Unknown; use with caution.
Sofosbuvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the elderly. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required in mild or moderate renal impairment. Safety and efficacy have not been established in severe renal impairment (eGFR <30 mL/ min) or hemodialysis; no dose recommendation can be given.	No dosage adjustment required. Safety and efficacy have not been established in patients with decompensated cirrhosis.	B*	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Combination Products					
Ledipasvir/ sofosbuvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the elderly. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required in mild or moderate renal impairment. Safety and efficacy have not been established in severe renal impairment (eGFR <30 mL/ minute) or ESRD requiring hemodialysis; no dose recommendation can be given.	No dosage adjustment required. Safety and efficacy have not been established in patients with decompensated cirrhosis.	B	Unknown; use with caution.
Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the elderly. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required in mild, moderate or severe renal impairment.	No dosage adjustment required in mild hepatic impairment (Child-Pugh A). Not recommended in moderate hepatic impairment (Child-Pugh B). Contraindicated in severe hepatic impairment (Child-Pugh C).	B*	Unknown; use with caution.

eGFR=estimated glomerular filtration rate, ESRD=end stage renal disease
*Ribavirin has a pregnancy category of X. The use of any direct acting hepatitis C antiviral regimen containing ribavirin is contraindicated in pregnancy.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-6]

Adverse Event(s)	Boceprevir*	Simeprevir	Sofosbuvir	Ledipasvir/sofosbuvir	Ombitasvir/paritaprevir/ritonavir/dasabuvir‖
Alopecia	27/22	-	-	-	-
Anemia	50/45	-	6§ to 21†	-	-
Arthralgia	19/23	-	-	-	-
Asthenia	15/21	-	5† to 21§	-	4/9
Chills	34/33	-	2§,‡ to 17†	-	-
Decreased appetite	25/26	-	6*‡ to 18†	-	-
Diarrhea	25/24	-	9‡ to 12§,†	3 to 7	-
Dizziness	19/16	-	-	-	-
Dry mouth	11/15	-	-	-	-
Dry skin	18/22	-	-	-	-
Dysgeusia	35/44	-	-	-	-
Dyspnea	8/11	12	-	-	-
Fatigue	58/55	-	30* to 59†	13 to 18	-
Headache	-	-	24‡ to 36†	11 to 17	-
Influenza like illness	-	-	3‡ to 16†	-	-
Insomnia	34/30	-	15‡ to 25†	3 to 6	5/12
Irritability	22/21	-	10*,‡ to 13†	-	-
Myalgia	-	16	6‡ to 14†	-	-
Nausea	46/43	22	13* to 34†	6 to 9	8/16
Neutropenia	25/14	-	<1*,‡ to 17†	-	-
Pruritus	-	22	11‡ to 27*	-	7/13
Pyrexia	-	-	4*,‡ to 18†	-	-
Rash	17/16	28	8‡ to 18†	-	-
Vomiting	20/15	-	-	-	-

-Incidence not reported or <1%
*Reported as: treatment-naïve patients/previous treatment failures (percent/percent).
†Sofosbuvir plus peginterferon alfa and weight-based ribavirin for 12 weeks treatment regimen.
‡Sofosbuvir plus weight-based ribavirin for 12 weeks treatment regimen.
§Sofosbuvir plus weight-based ribavirin for 24 weeks treatment regimen.
‖Reported as: (ombitasvir/paritaprevir/ritonavir/dasabuvir)/(ombitasvir/paritaprevir/ritonavir/dasabuvir + ribavirin)

Contraindications

When direct acting hepatitis C antivirals are used in combination with pegylated interferon alfa and/or ribavirin, contraindications to those agents also apply to the direct acting hepatitis C antivirals. Ribavirin may cause birth defects and/or death of the exposed fetus and is contraindicated in pregnancy.[1-3,5] Refer to individual label information for pegylated interferon alfa and ribavirin for contraindications associated with those agents.[27-35]

Table 7. Contraindications[1-5]

Contraindications	Boceprevir	Simeprevir	Sofosbuvir	Ledipasvir/ sofosbuvir	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir
Coadministration with drugs that are highly dependent on cytochrome P450 (CYP) 3A for clearance					a
Coadministration with drugs that are highly dependent on cytochrome P450 (CYP) 3A4/5 for clearance	a				
Coadministration with drugs that strongly induce CYP2C8					a
Coadministration with drugs that strongly induce CYP3A					a
Coadministration with drugs that strongly induce CYP3A4/5	a				
Coadministration with drugs that strongly inhibit CYP2C8					a
Hepatic impairment, severe					a
Hypersensitivity to the drug or any component	a	a	a	a	a

Warnings/Precautions

Table 8. Warnings/Precautions[1-5]

Warnings/Precautions	Boceprevir	Simeprevir	Sofosbuvir	Ledipasvir/ sofosbuvir	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir
Alanine transaminase (ALT) increases to five times the upper limit has been reported in 1% of patients; significantly more frequent in females ethinyl estradiol-containing medications					a
Anemia and pancytopenia has been reported (with ribavirin/peginterferon)	a				
Embryofetal toxicity (use with ribavirin and peginterferon alfa)	a	a	a		a
Hypersensitivity reactions, severe/acute (with ribavirin/peginterferon)					
Monotherapy not recommended; must be used in combination therapy	a	a	a		
P-gp inducers (potent) reduce therapeutic effect			a	a	
Photosensitivity reactions have been reported (with ribavirin/peginterferon)		a			
Rash has been reported (use with ribavirin and peginterferon alfa)		a			

When used in combination with peginterferon alfa or ribavirin the warnings and associated with those agents are also applicable to the hepatitis C direct acting antivirals. Refer to the individual labels for these agents for a complete list of warnings and precautions associated with them.[27-35] The Black Box Warnings for those agents are outlined below.

Black Box Warning for peginterferon alfa-2a (Pegasys®) and peginterferon alfa-2b (Peg Intron®, Sylatron®)[27-29]

WARNING
Alfa interferons, including peginterferon alfa-2a and alfa-2b, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping peginterferon alfa-2a or alfa-2b therapy. Use with ribavirin: ribavirin may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease.

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Black Box Warnings for ribavirin (Copegus®, Moderiba®, Moderiba Pak®, Rebetol®, Ribasphere®, Ribasphere RibaPak® and Ribatab®)[30-35]

WARNING
Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication. The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as six months. Therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for six months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the six month post treatment follow up period.

Drug Interactions

Table 9a. Drug Interactions – Protease Inhibitors (Not All Inclusive)[1,2,6]

Generic Name	Interacting Medication or Disease	Potential Result
Hepatitis C protease inhibitors (all)	Barbiturates	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response.
Hepatitis C protease inhibitors (all)	HMG-CoA Reductase Inhibitors	HMG-CoA Reductase Inhibitors plasma concentrations may be elevated, increasing the pharmacologic effects and risk of myopathy and rhabdomyolysis. Coadministration of boceprevir or telaprevir with either lovastatin or simvastatin is contraindicated. Coadministration of atorvastatin with telaprevir is contraindicated. Atorvastatin dose should not exceed 40 mg daily when coadministered with either boceprevir or simeprevir. Rosuvastatin dose should not exceed 10 mg daily when coadministered with simeprevir.
Hepatitis C protease inhibitors (all)	Human Immunodeficiency Virus Protease Inhibitors	Hepatitis C protease inhibitor plasma concentrations may be altered by certain Human Immunodeficiency Virus Protease Inhibitors. Co-administration of simeprevir with any Human Immunodeficiency Virus Protease Inhibitor, with or without ritonavir, is not recommended. Co-administration of boceprevir or telaprevir with either darunavir/ritonavir or lopinavir/ritonavir is not recommended. Co-administration of boceprevir with atazanavir/ritonavir is not recommended. Co-administration of telaprevir with fosamprenavir/ritonavir is not recommended.
Hepatitis C protease inhibitors (all)	Hydantoins	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Hydantoin concentrations may be elevated or reduced.
Hepatitis C protease inhibitors (all)	Non-Nucleoside Reverse Transcriptase Inhibitors	Hepatitis C protease inhibitor plasma concentrations may be altered by certain Non-Nucleoside Reverse Transcriptase Inhibitors. Co-administration of boceprevir or simeprevir with efavirenz is not recommended. Telaprevir dosage should be increased to 1,125 mg every eight hours when co-administered with efavirenz. Co-administration of any Hepatitis C protease inhibitor with nevirapine is not recommended. Co-administration of simeprevir with delavirdine or etravirine is not recommended.
Hepatitis C protease inhibitors (all)	Rifamycins	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Rifamycin concentrations may be elevated by boceprevir or telaprevir, increasing the risk of adverse reactions.
Hepatitis C protease inhibitors (all)	Carbamazepine	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response.
Hepatitis C protease inhibitors (all)	Cisapride	Cisapride plasma concentrations may be elevated, increasing the pharmacologic effects and risk of cardiac arrhythmias.
Hepatitis C protease inhibitors (all)	St. John's Wort	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response
Boceprevir	α-1 adrenergic blockers	α-1 adrenergic blocker plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Boceprevir	Benzodiazepines	Plasma concentrations of certain benzodiazepines may be elevated, increasing the pharmacologic effects and risk of severe

Generic Name	Interacting Medication or Disease	Potential Result
		sedation and prolonged respiratory depression.
Boceprevir	Contraceptives, hormonal	Plasma concentrations of certain progestins may be elevated, increasing the risk of hyperkalemia. Estrogen concentrations may be reduced, increasing the risk of unintended pregnancy.
Boceprevir	Cyclosporine	Cyclosporine plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Boceprevir	Ergot derivatives	Ergot derivative plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Boceprevir	Phosphodiesterase Type 5 Inhibitors	Phosphodiesterase type 5 inhibitor plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions. Coadministration with a phosphodiesterase type 5 inhibitor for pulmonary hypertension is contraindicated. Coadminister phosphodiesterase type 5 inhibitors for erectile dysfunction with caution.
Boceprevir	Lomitapide	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity
Boceprevir	Pimozide	Pimozide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of life-threatening cardiac arrhythmias.
Boceprevir	Tacrolimus	Tacrolimus plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including QT prolongation.
Simeprevir	Antifungals	Simeprevir plasma concentrations may be increased by certain antifungals. Co-administration with systemic itraconazole, fluconazole, ketoconazole, posaconazole, and voriconazole is not recommended.
Simeprevir	Clarithromycin, erythromycin, telithromycin	Simeprevir plasma concentrations may be increased. Erythromycin plasma concentration may also be increased. Co-administration with clarithromycin, erythromycin or telithromycin is not recommended.
Simeprevir	Dexamethasone	Simeprevir plasma concentrations may be reduced by systemic dexamethasone. Co-administration with systemic dexamethasone is not recommended.
Simeprevir	Elvitegravir/cobicistat/ emtricitabine/tenofovir	Simeprevir plasma concentrations may be increased by cobicistat-containing product elvitegravir/cobicistat/emtricitabine /tenofovir. Co-administration with cobicistat-containing product is not recommended.
Simeprevir	Oxcarbazepine	Simeprevir plasma concentrations may be reduced, leading to loss of virologic response.

Table 9b. Drug Interactions – Polymerase Inhibitors (Not All Inclusive)[3,4,6]

Generic Name	Interacting Medication or Disease	Potential Result
Ledipasvir	Antacids: aluminum and magnesium hydroxide	Coadministration may result in decreased plasma concentrations of ledipasvir. It is recommended to separate antacid and ledipasvir/sofosbuvir administration by four hours.
Ledipasvir	H_2-receptor antagonists: famotidine	H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from ledipasvir/sofosbuvir at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.

Generic Name	Interacting Medication or Disease	Potential Result
Ledipasvir	Proton-pump inhibitors: omeprazole	Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with ledipasvir/sofosbuvir under fasted conditions.
Ledipasvir	Antiarrhythmics: digoxin	Coadministration with digoxin may increase the concentration of digoxin. Monitor therapeutic concentration of digoxin during coadministration.
Ledipasvir, Sofosbuvir	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may result in decreased plasma concentrations of sofosbuvir and/or ledipasvir leading to loss of therapeutic effect of sofosbuvir. Coadministration is not recommended.
Ledipasvir, Sofosbuvir	Rifampin, rifabutin, rifapentine	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.
Ledipasvir, Sofosbuvir	St. John's wort (*Hypericum perforatum*)	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.
Ledipasvir, Sofosbuvir	Tipranavir/ritonavir	Coadministration may result in decreased plasma concentrations of sofosbuvir and/or ledipasvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.

Table 9c. Drug Interactions Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir - (Not All Inclusive)[5,6]

Generic Name	Interacting Medication	Potential Result
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Alfuzosin	Increased alfuzosin concentration, increased risk for hypotension; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Anticonvulsants (carbamazepine, phenytoin, phenobarbital)	Decreased ombitasvir/paritaprevir/ritonavir/dasabuvir concentration; loss of therapeutic effect; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Gemfibrozil	Increased concentration of dasabuvir (10x); increased risk of QT prolongation; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Rifampin	Decreased ombitasvir/paritaprevir/ritonavir/dasabuvir concentration; loss of therapeutic effect; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Ergot derivatives (ergotamine, dihydroergotamine, ergonovine, methylergonovine)	Increased ergot derivative concentrations; acute ergot toxicity characterized by vasospasm and tissue ischemia; contraindicated.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	St. John's Wort	Decreased ombitasvir/paritaprevir/ritonavir/dasabuvir concentration; loss of therapeutic effect; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Statins (lovastatin, simvastatin)	Increased concentrations of lovastatin and simvastatin; potential for myopathy; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Efavirenz	Coadministration was poorly tolerated and resulted in liver enzyme elevations.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Sildenafil	Increased concentrations of sildenafil; potential for visual disturbances, hypotension, priapism and syncope; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Sedatives/hypnotics (triazolam midazolam [oral])	Coadministration may cause large increases in benzodiazepine concentration. The potential exists for serious and/or life threatening events such as sedation or respiratory depression; contraindicated

Generic Name	Interacting Medication	Potential Result
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Antiarrhythmics (amiodarone, bepridil, disopyramide, flecainide, lidocaine, mexiletine, propafenone, quinidine)	Decreased concentration of antiarrhythmics; caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Ketoconazole	Increased ketoconazole concentration; limit max daily dose of ketoconazole to 200 mg per day
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Voriconazole	Decreased voriconazole concentration; coadministration not recommended (benefit-to-risk justifies use)
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Amlodipine	increased concentration of amlodipine; dose adjust
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Fluticasone	Increased fluticasone concentration; may alter cortisol levels; use an alternate corticosteroid
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Furosemide	Furosemide concentration increased, dose adjust
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Atazanavir/ritonavir, lopinavir/ritonavir	Increased concentrations of paritaprevir; only coadminister atazanavir without ritonavir and limit to 300 mg in the morning; do not coadminister lopinavir/ritonavir
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Darunavir/ritonavir	Decreased concentration of darunavir; coadministration is not recommended
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Rilpivirine	Increased concentration of rilpivirine; increased risk of QT interval prolongation
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Statins (rosuvastatin, pravastatin)	Increased concentrations of the statins; limit dose to 10 mg (rosuvastatin) and 40 mg (pravastatin)
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Cyclosporine	Increased concentration of cyclosporin; when coadministered, reduce cyclosporine dose to 1/5th of the current dose. Measure cyclosporine blood concentrations to determine subsequent dose modifications. Frequent assessment of renal function and cyclosporine-related side effects is recommended.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Tacrolimus	Increased concentration of tacrolimus; when coadministered, reduce tacrolimus dose. Measure tacrolimus blood concentrations to determine subsequent dose modifications. Frequent assessment of renal function and tacrolimus-related side effects is recommended.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Salmeterol	Increased concentration of salmeterol; increased risk of cardiovascular event; coadministration not recommended
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Buprenorphine (±naloxone)	Increased concentration of buprenorphine; no dose adjustment required; monitor for adverse effects
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Omeprazole	Decreased concentration of omeprazole; limit dose to 40 mg or less
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Alprazolam	increased concentration of alprazolam; monitor for side effects; dose adjust based on clinical response

Dosage and Administration

The overall duration of therapy with boceprevir is response-guided based on hepatitis C virus (HCV) ribonucleic acid (RNA) levels at certain treatment weeks. While the overall duration of therapy with simeprevir is not response-guided, the stopping rules which allow for early discontinuation of therapy in patients with inadequate on-treatment virologic response, apply to both remaining protease inhibitors when used in combination with peginterferon alfa and ribavirin. In general, patients with inadequate viral response are unlikely to achieve sustained virologic response, and may develop treatment-emergent resistance substitutions. There are no stopping rules associated with simeprevir and sofosbuvir dual therapy, sofosbuvir (+ ribavirin ± peginterferon alfa), ledipasvir/ sofosbuvir, or ombitasvir/paritaprevir/ritonavir/dasabuvir (± ribavirin). General dosing recommendations for protease inhibitors are outlined in Table 8, while the recommendations for response-guided therapy and/or stopping rules are outlined in Tables 9 and 10.[1-2]

Boceprevir is added to peginterferon alfa and ribavirin after a four week lead-in period of peginterferon alfa and ribavirin alone (treatment weeks one through four), and is administered for either 24 or 32 weeks depending on the patient's treatment history and HCV RNA levels.[1] Simeprevir is initiated with peginterferon alfa and ribavirin and administered for 12 weeks regardless of treatment history or HCV RNA levels.[2] When used in combination with sofosbuvir, simeprevir dual therapy is given for 12 or 24 weeks depending on cirrhosis status.[2]

Table 10. Dosing and Administration[1-6]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Products			
Boceprevir	Treatment of chronic hepatitis genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers: Capsule: initial, after four weeks of peginterferon alfa and ribavirin administer 800 mg TID (every seven to nine hours) with food (a meal or light snack)	Safety and efficacy in children have not been established.	Capsule: 200 mg
Simeprevir	Treatment on chronic hepatitis C genotype 1 infection as a component of a combination antiviral treatment regimen with peginterferon alfa plus ribavirin: Capsule: 150 mg QD with food for 12 weeks Treatment on chronic hepatitis C genotype 1 infection as a component of a combination antiviral treatment regimen with sofosbuvir: Capsule: 150 mg QD with food for 12 or 24 weeks	Safety and efficacy in children have not been established.	Capsule: 150 mg
Sofosbuvir	Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment in combination with ribavirin alone (without peginterferon alfa) can be considered for hepatitis C patients with genotype 1 infection who are ineligible to receive an interferon-based regimen: Tablet: 400 mg QD for 12 weeks (with peginterferon alfa and ribavirin) or 24 weeks (with ribavirin alone in patients ineligible to receive an interferon-based regimen) Treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin: Tablet: 400 mg QD for 12 weeks	Safety and efficacy in children have not been established.	Tablet: 400 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin: Tablet: 400 mg QD for 12 weeks (genotype 2) or 24 weeks (genotype 3) Prevention of post-transplant HCV reinfection in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection: Tablet: 400 mg QD for up to 48 weeks or until liver transplantation, whichever occurs first		
Combination Products			
Ledipasvir/ sofosbuvir	Treatment of chronic HCV genotype 1 infection: Tablet: 90/400 mg QD for 12 weeks (treatment-naïve with or without cirrhosis* or treatment-experienced without cirrhosis) or 90/400 mg QD for 24 weeks (treatment-experienced with cirrhosis).	Safety and efficacy in children have not been established.	Tablet: 90/400 mg
Ombitasvir/paritaprevir/ ritonavir/ dasabuvir	Treatment of genotype 1a chronic HCV infection without cirrhosis Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet BID with ribavirin for 12 weeks Treatment of genotype 1a chronic HCV infection with cirrhosis Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet BID with ribavirin for 24 weeks (12 weeks may be considered for some patients based on prior treatment history) Treatment of genotype 1b chronic HCV infection without cirrhosis Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet BID for 12 weeks Treatment of genotype 1b chronic HCV infection with cirrhosis Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet BID with ribavirin for 12 weeks Treatment of genotype 1 chronic HCV infection in liver transplant recipients with normal hepatic function and mild fibrosis (F2 or lower) Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet twice daily with ribavirin for 24 weeks	Safety and efficacy in children have not been established.	Tablet: Ombitasvir/ paritaprevir/ ritonavir (12.5/75/50 mg) Dasabuvir (250 mg)

BID=twice daily, HCV=hepatitis C virus, HIV=human immunodeficiency virus, QD=once daily, TID=three times a day
*Ledipasvir/sofosbuvir may be considered for 8 weeks of therapy in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.

Table 11. Boceprevir Response-guided Treatment in Patients Without Cirrhosis[1]

	Assessment* (HCV RNA Results†)		Recommendation‡
	At Treatment Week Eight	At Treatment Week 24	
Treatment-Naïve Patients	Undetectable	Undetectable	Complete boceprevir, peginterferon alfa and ribavirin at treatment week 28
	Detectable	Undetectable	Continue boceprevir, peginterferon alfa and ribavirin and finish through treatment week 36; then administer peginterferon alfa and ribavirin and finish through treatment week 48
Previous Partial Responders or Relapsers	Undetectable	Undetectable	Complete boceprevir, peginterferon alfa and ribavirin at treatment week 36
	Detectable	Undetectable	Continue boceprevir, peginterferon alfa and ribavirin and finish through treatment week 36; then administer peginterferon alfa and ribavirin and finish through treatment week 48
Previous Null Responders	Detectable or undetectable	Undetectable	Continue all three medications and finish through week 48.

HCV=hepatitis C virus, RNA=ribonucleic acid
*If the patient has hepatitis C virus (HCV) ribonucleic acid (RNA) results ≥1,000 IU/mL at treatment week 8, discontinue boceprevir, peginterferon alfa and ribavirin. If the patient has HCV-RNA results ≥100 IU/mL at treatment week 12, discontinue boceprevir, peginterferon alfa and ribavirin. If the patient has confirmed, detectable HCV-RNA at treatment week 24, then discontinue boceprevir, peginterferon alfa and ribavirin.
†In clinical trials, HCV RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25.0 IU/mL and a limit of detection of 9.3 IU/mL.
‡Includes the four week lead in phase of peginterferon and ribavirin therapy.

Consideration should be given to treating previously untreated patients who are poorly interferon responsive (as determined at treatment week four) with four weeks peginterferon alfa and ribavirin followed by 44 weeks of boceprevir in combination with peginterferon alfa and ribavirin in order to maximize rates of sustained virologic response. Patients with cirrhosis should receive four weeks of peginterferon alfa and ribavirin followed by 44 weeks of boceprevir in combination with peginterferon alfa and ribavirin.[1]

Table 12. Simeprevir Duration of Treatment[2]

	Recommendations		
	Triple Therapy (Simeprevir, Peginterferon alfa and Ribavirin)*	Dual Therapy (Peginterferon alfa and Ribavirin)*	Total Treatment Duration*
Treatment-Naïve and Prior Relapse Patients Including Those with Cirrhosis	First 12 weeks	Additional 12 weeks	24 weeks
Prior Partial and Null Responder Patients Including Those with Cirrhosis	First 12 weeks	Additional 36 weeks	48 weeks

*If the patient has hepatitis C virus (HCV) ribonucleic acid (RNA) results ≥25 IU/mL at treatment week four or 12, discontinue simeprevir, peginterferon alfa and ribavirin. If the patient has HCV RNA results ≥25 IU/mL at treatment week 24, then discontinue peginterferon alfa and ribavirin. In clinical trials, HCV RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25.0 IU/mL and a limit of detection of 15 IU/mL.

Clinical Guidelines

Table 13. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases, Infectious Diseases Society of America, and International Antiviral Society-USA: **Recommendations for testing, managing, and treating hepatitis C (2014)**[26]	· This summary will focus on the recommendations for treatment of hepatitis C virus (HCV) infection Goal of Treatment · 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 a sustained virologic response (SVR). When and in Whom to Initiate Treatment · Treatment is recommended for patients with chronic HCV infection. · Immediate treatment is assigned the highest priority for those patients with the highest risk for severe complications o Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4) o Liver transplant recipients o Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis) o Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis · Based on available resources, immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority. o Fibrosis (Metavir F2) o HIV-1 coinfection o Hepatitis B virus (HBV) coinfection o Other coexistent liver disease (e.g., [NASH]) o Debilitating fatigue o Type 2 Diabetes mellitus (insulin resistant) o Porphyria cutanea tarda · An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended. · Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred. Initial Treatment of HCV Infection (treatment naïve) · Genotype 1a o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg plus weight-based ribavirin for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) o Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without ribavirin for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) · Genotype 1b (three options with similar efficacy are recommended) o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg for 12 weeks § The addition of weight-based ribavirin is recommended in patients with cirrhosis o Daily sofosbuvir 400 mg plus simeprevir 150 mg for 12 weeks · The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 1

Clinical Guideline	Recommendation(s)
	o Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks o Peginterferon alfa and ribavirin with or without sofosbuvir, simeprevir, telaprevir or boceprevir for 12 to 48 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral · Genotype 2 o Daily sofosbuvir 400 mg and weight based ribavirin for 12 weeks § extending to 16 weeks is recommended in patients with cirrhosis o There are no alternate regimens recommended for treatment-naïve patients with hepatitis C genotype 2 · The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 2 o Peginterferon alfa and ribavirin for 24 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir-, boceprevir-, or ledipasvir-containing regimens · Genotype 3 o Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks o Alternate: Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks is acceptable for interferon-eligible, treatment-naïve patients with HCV genotype 3 · The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 3 o Peginterferon alfa and ribavirin for 24 to 48 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir-, boceprevir-, or ledipasvir-containing regimens · Genotype 4 o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 and weight-based ribavirin for 12 weeks o Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks o Alternate: § Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks § Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without weight-based ribavirin for 12 weeks · The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 4 o Peginterferon alfa and ribavirin with or without simeprevir for 24 to 48 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens · Genotype 5 o Daily sofosbuvir 400 mg and weight-based ribavirin for 12 weeks o Alternate: Weekly peginterferon alfa plus weight-based ribavirin for 48 weeks · Genotype 6 o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Alternate: Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks · The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 5 or 6 o monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens

Clinical Guideline	Recommendation(s)
	Retreatment After Failed Therapy (peginterferon alfa and ribavirin) · Genotype 1a (no cirrhosis); o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice daily dasabuvir 250 mg and weight-based ribavirin for 12 weeks o Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without weigh-based ribavirin for 12 weeks · Genotype 1b (no cirrhosis); failed peginterferon alfa and ribavirin o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice daily dasabuvir 250 mg o Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without weigh-based ribavirin for 12 weeks · Genotype 1a or 1b (with cirrhosis); failed peginterferon alfa and ribavirin o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 24 weeks o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg plus weight-based ribavirin for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice daily dasabuvir 250 mg and weight-based ribavirin for 24 weeks (genotype 1a) or 12 weeks (genotype 1b) o Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without weight-based ribavirin for 24 weeks · Genotype 2 o Daily sofosbuvir 400 mg and weight-based ribavirin for 12 to 16 weeks o Alternate (peginterferon alfa eligible): Retreatment with daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks · The following regimens are NOT recommended for patients with HCV genotype 2 who have failed peginterferon alfa and ribavirin o Peginterferon alfa and ribavirin with or without telaprevir or boceprevir o Fixed-dose combination ledipasvir/sofosbuvir 90/400 mg o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral · Genotype 3 o Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks o Alternate (peginterferon alfa eligible): Retreatment with daily sofosbuvir 400 mg and wight-based ribavirin plus weekly peginterferon alfa for 12 weeks · The following regimens are NOT recommended for patients with HCV genotype 3 who have failed peginterferon alfa and ribavirin o Peginterferon alfa and ribavirin for 24 weeks to 48 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir-, boceprevir-, or simeprevir-based regimens · Genotype 4 o Daily ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily paritaprevir/ritonavir/ombitasvir 150/100/25 mg and weight-based ribavirin for 12 weeks o Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks o Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks · The following regimens are NOT recommended for patients with HCV genotype 4 who have failed peginterferon alfa and ribavirin o Peginterferon alfa and ribavirin with or without telaprevir or boceprevir o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral

Clinical Guideline	Recommendation(s)
	Retreatment After Failed Therapy (sofosbuvir-containing regimen) · Patients with advanced fibrosis o Patients without an urgent need for HCV treatment should defer antiviral therapy pending additional data or consider treatment within clinical trial settings. o Daily ledipasvir/sofosbuvir 90/400 mg with or without weight-based ribavirin for 24 weeks Retreatment After Failed Therapy (peginterferon alfa, ribavirin and an HCV protease inhibitor regimen) · Genotype 1 (no cirrhosis) o Daily ledipasvir/sofosbuvir 90/400 mg for 12 weeks · Genotype 1 (with cirrhosis) o Daily ledipasvir/sofosbuvir 90/400 mg for 24 weeks o Daily ledipasvir/sofosbuvir 90/400 mg plus weight-based ribavirin for 12 weeks · The following regimens are NOT recommended for patients with HCV genotype 1 who have failed an HCV protease inhibitor containing regimen o Any regimen containing peginterferon alfa, including: § Simeprevir, ribavirin and peginterferon alfa § Sofosbuvir, ribavirin and peginterferon alfa § Telaprevir or boceprevir, ribavirin and peginterferon alfa § Ribavirin and peginterferon alfa dual therapy o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Any interferon-free regimen containing an HCV protease inhibitor § Simeprevir or Paritaprevir Retreatment After Failed Therapy (genotypes 5 and 6) · Few data are available to help guide decision making for patients infected with HCV genotype 5 or 6. · Recommendations for genotypes 5 and 6 do not specify which treatments have been failed previously. · Genotype 5 o Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks o Alternate: Weekly peginterferon alfa plus weight-based ribavirin for 48 weeks · Genotype 6 o Daily ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Alternate (peginterferon eligible): Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon for 12 weeks · The following regimens are NOT recommended for patients with HCV genotypes 5 or 6 who have failed previous therapy o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens Monitoring at Onset, During Treatment and After Completion of HCV Therapy · Recommended Assessments prior to starting antiviral therapy o Assessment of potential drug-drug interactions o Laboratory tests within 12 weeks prior to starting: § Complete blood count (CBC); international normalized ratio (INR) § Hepatic function § Thyroid-stimulating hormone (TSH) (if interferon is used)

Clinical Guideline	Recommendation(s)
	§ Calculated glomerular filtration rate (GFR) o Laboratory tests any time prior to starting: § HCV genotype and subtype § Quantitative HCV viral load, except in the circumstance that a quantitative viral load will influence duration of therapy · Monitoring during antiviral therapy o Routine monitoring for HCV drug resistance-associated variants during therapy is not recommended o Clinic visits or telephone contact are recommended as clinically indicated during treatment to ensure medication adherence and to monitor for adverse events and potential drug-drug interactions with newly prescribed medications. o Laboratory § After four weeks of treatment or as clinically indicated: · CBC, creatinine level, calculated GFR, hepatic function § Every 12 weeks of treatment (for patients receiving interferon) · TSH o More frequent assessment for drug-related toxic effects (eg, CBC for patients receiving RBV) is recommended as clinically indicated. o Prompt discontinuation of therapy is recommended for § A 10-fold increase in alanine aminotransferase (ALT) activity at week four § Any increase in ALT of less than 10-fold at week 4 that is accompanied by any weakness, nausea, vomiting, or jaundice, or accompanied by increased bilirubin, alkaline phosphatase, or INR. Asymptomatic increases in ALT of less than 10-fold elevated at week four should be closely monitored and repeated at week six and week eight. o Quantitative HCV viral load testing is recommended after 4 weeks of therapy and at 12 weeks following completion of therapy. § Antiviral therapy should NOT be interrupted or discontinued if HCV RNA levels are not performed or available during treatment. o Quantitative HCV viral load testing can be considered at the end of treatment and 24 weeks or longer following the completion of therapy. · Recommendations for discontinuation of treatment due to lack of efficacy o HCV viral load is detectable at week four, repeat quantitative HCV viral load after two additional weeks of treatment (treatment week six). § If quantitative HCV viral load has increased by greater than 10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week six (or thereafter), discontinue HCV treatment. o The significance of a positive HCV RNA test result at week 4 that remains positive, but lower, at week six or week eight is unknown. § No recommendation to stop therapy or extend therapy can be provided at this time. · Recommended monitoring in patients who have failed to achieve a sustained virologic response: o Disease progression assessment every 6 to 12 months with a hepatic function panel, CBC, and INR is recommended. o Surveillance for hepatocellular carcinoma with ultrasound testing every 6 months is recommended for patients with advanced fibrosis (i.e., Metavir stage F3 or F4). o Endoscopic surveillance for esophageal varices is recommended if cirrhosis is present.

Clinical Guideline	Recommendation(s)
	o Evaluation for retreatment is recommended as effective alternative treatments become available. · Recommended follow-up for patients who achieve a sustained virologic response o For patients who do not have advanced fibrosis (i.e., those with Metavir stage F0-F2), recommended follow-up is the same as if they were never infected with HCV. o Assessment for HCV recurrence or reinfection is recommended only if the patient has ongoing risk for HCV infection or otherwise unexplained hepatic dysfunction develops. In such cases, a quantitative HCV RNA assay rather than an anti-HCV serology test is recommended to test for HCV recurrence or reinfection. o Surveillance for hepatocellular carcinoma with twice-yearly ultrasound testing is recommended for patients with advanced fibrosis (i.e., Metavir stage F3 or F4) who achieve a sustained virologic response. o A baseline endoscopy is recommended to screen for varices if cirrhosis is present. Patients in whom varices are found should be treated and followed up as indicated. o Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving a sustained virologic response. · Prospective monitoring for HCV recurrence among patients who achieved a sustained virologic response and who are receiving immunosuppressive treatments (systemic corticosteroids, antimetabolites, chemotherapy, etc.) is NOT routinely recommended Special Populations - Pregnancy: · Monitoring for pregnancy-related issues prior to and during antiviral therapy (treatment includes ribavirin) o Women of childbearing age should be cautioned not to become pregnant while receiving RBV-containing antiviral regimens, and for up to six months after stopping. o Serum pregnancy testing is recommended for women of childbearing age prior to beginning treatment with a regimen that includes ribavirin. o Assessment of contraceptive use and of possible pregnancy is recommended at appropriate intervals during (and for six months after) ribavirin treatment for women of childbearing potential, and for female partners of men who receive ribavirin treatment. · The following regimens are NOT recommended with regard to pregnancy-related issues o Treatment is NOT recommended for pregnant women or for women who are unwilling to adhere to use of adequate contraception, including those who are receiving ribavirin themselves or are sexual partners of male patients who are receiving ribavirin. o Female patients who have received ribavirin and sexual partners of male patients who have received ribavirin should not become pregnant for at least 6 months after stopping ribavirin. Special Populations – Human Immunodeficiency Virus (HIV)/HCV Coinfection · HIV/HCV-coinfected persons should be treated and re-treated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications. · The following regimens are NOT recommended for treatment-naïve or treatment-experienced HIV/HCV-coinfected patients

Clinical Guideline	Recommendation(s)
	o Peginterferon alfa and ribavirin with or without simeprevir, telaprevir or boceprevir for 24 to 48 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral · When switching antiviral drugs as needed for drug interactions between HIV and HCV antivirals, consult an HIV practitioner. o For the HIV antiretroviral and HCV direct-acting antiviral combinations not addressed below, expert consultation is recommended. · For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended · Ledipasvir/sofosbuvir o Ledipasvir increases tenofovir levels, creatine clearance (CrCl) should be considered. § Avoid ledipasvir if CrCl <60 mL/min. § Avoid if tenofovir is boosted by ritonavir (pending further data) unless antiretroviral regimen cannot be changed and the urgency of treatment is high. · Paritaprevir/ritonavir/ombitasvir/dasabuvir o Use with antiretroviral drugs with no substantial interactions: raltegravir (and probably dolutegravir), enfuvirtide, tenofovir, emtricitabine, lamivudine and atazanavir o The dose of ritonavir used for boosting of HIV protease inhibitors may need to be adjusted (or held) when administered with this combination and then restarted when HCV treatment is completed. § Administer the HIV protease inhibitor at the same time as the fixed-dose HCV combination. · Simeprevir o Only use with antiretrovirals in which it does not have clinically significant interactions: raltegravir (and probably dolutegravir), rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine and abacavir · The following are NOT recommended or should not be used: o Antiretroviral treatment interruption to allow HCV therapy o Ledipasvir/sofosbuvir with cobicistat and elvitegravir o Sofosbuvir or ledipasvir/sofosbuvir with tipranavir o Paritaprevir/ritonavir/ombitasvir/dasabuvir with efavirenz, rilpivirine, darunavir or ritonavir-boosted lopinavir o Paritaprevir/ritonavir/ombitasvir/dasabuvir should not be used in HIV/HCV-coinfected patients who are not taking antiretroviral therapy o Simeprevir with efavirenz, etravirine, nevirapine, cobicistat or any HIV protease inhibitors o Ribavirin with didanosine, stavudine or zidovudine Special Populations - Decompensated Cirrhosis · Patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh [CTP] class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center). o The following regimens should only be used by highly experienced HCV practitioners. · Genotype 1 or 4 (patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma); o Daily ledipasvir/sofosbuvir 90/400 mg and ribavirin (initial dose 600 mg, increased as tolerated) for 12 weeks o Alternate (anima or ribavirin intolerant): Daily Ledipasvir/sofosbuvir 90/400 mg for 24 weeks

Clinical Guideline	Recommendation(s)
	o Alternate (prior failure with a sofosbuvir-based regimen): Daily ledipasvir/sofosbuvir 90/400 mg and ribavirin (initial dose 600 mg, increased as tolerated) for 24 weeks · Genotype 2 or 3 (patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma) o Daily sofosbuvir 400 mg and weight-based ribavirin (with consideration of the patient's CrCl and hemoglobin level) for up to 48 weeks · The following regimens are NOT recommended for patients with decompensated cirrhosis: o Any interferon-based therapy o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir-, boceprevir-, or simeprevir-based regimens o Paritaprevir-, ombitasvir-, or dasabuvir-based regimens Special Populations - Recurrent HCV Infection Post-Liver Transplantation · Genotype 1 or 4 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Daily ledipasvir/sofosbuvir 90/400 mg with weight-based ribavirin for 12 weeks o Alternative (ribavirin intolerant): ledipasvir/sofosbuvir 90/400 mg for 24 weeks o Alternative (genotype 1 only): sofosbuvir 400 mg plus simeprevir 150 mg with or without weight-based ribavirin for 12 weeks o Alternative (genotype 1, including early [Metavir fibrosis stage F0-F2] recurrence): Daily paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg and weight-based ribavirin for 24 weeks · Genotype 1 or 4 infection in the allograft, liver transplant recipients (with decompensated cirrhosis), treatment-naïve or treatment-experienced o Daily ledipasvir/sofosbuvir 90/400 mg with a low initial dose of ribavirin (600 mg, increasing as tolerated) for 12 weeks · Genotype 2 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Daily sofosbuvir 400 mg plus weight-based ribavirin for 24 weeks · Genotype 2 infection in the allograft, liver transplant recipients (with decompensated cirrhosis), treatment-naïve or treatment-experienced o Daily sofosbuvir 400 mg with a low initial dose of ribavirin (600 mg, increased monthly by 200 mg/day as tolerated to a weight-based dose) for 24 weeks · Genotype 3 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Sofosbuvir 400 mg and weight-based ribavirin for 24 weeks · Genotype 3 infection in the allograft, liver transplant recipients (with decompensated cirrhosis), treatment-naïve or treatment-experienced o Sofosbuvir 400 mg and low initial dose of ribavirin (600 mg, increasing as tolerated) for 24 weeks · The following regimens are NOT recommended for treatment-naïve patients with compensated allograft HCV infection o Regimens containing peginterferon alfa o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens · The following regimens are NOT recommended for treatment-naïve patients with decompensated allograft HCV infection o Regimens containing peginterferon alfa o Regimens containing simeprevir

Clinical Guideline	Recommendation(s)
	o Daily paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg and weight-based ribavirin o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens Special Populations - Renal Impairment · Mild to moderate renal impairment (CrCl >30 mL/min) o Sofosbuvir: no dosage adjustment is required o Simeprevir: no dosage adjustment is required o Ledipasvir/sofosbuvir: no dosage adjustment is required o Paritaprevir/ritonavir/ombitasvir and dasabuvir: no dosage adjustment is required · For CrCL<30 mL/min, treatment can be contemplated after consultation with an expert; no safety and efficacy data are available for these patients Management of Acute HCV Infection · HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels · Preexposure or postexposure prophylaxis with antiviral therapy is NOT recommended. · Medical management and monitoring o Regular laboratory monitoring is recommended in the setting of acute HCV infection until the ALT level normalizes and HCV RNA becomes undetectable. o Monitoring HCV RNA (every 4 weeks to 8 weeks) for 6 to 12 months is recommended to detect spontaneous clearance of HCV infection. o Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults including hepatotoxic drugs and alcohol consumption and to reduce the risk of HCV transmission to others. o Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to injectable drug use. · Treatment for patients with acute HCV infection o If treatment is delayed, monitoring for spontaneous clearance is recommended for a minimum of 6 months. o If treatment is to begin during the acute infection period, monitor HCV RNA for at least 12 to 16 weeks to allow for spontaneous clearance before starting treatment. o Treatment is NOT recommended if HCV spontaneously clears. o Treatment with the same standard regimens are recommended for chronic and acutely-infected patients § Alternate (peginterferon eligible): Peginterferon alfa with or without ribavirin for 16 weeks (genotype 2 or 3 with a rapid virologic response) to 24 weeks (genotype 1).

Conclusions

The direct acting hepatitis C antiviral and combination products are all Food and Drug Administration (FDA)-approved for the treatment of chronic hepatitis C virus (HCV) infection; although, differences in indications exist relating to use in specific genotypes, with certain combination therapies and other patient factors.[1-5] The hepatitis C protease inhibitors boceprevir (Victrelis®) and simeprevir (Olysio®) both work via inhibition of the HCV NS3/4A protease of HCV genotype 1a and 1b thus preventing replication of HCV host cells.[1-2] Similarly, sofosbuvir (Sovaldi®) inhibits HCV NS5B polymerase which also prevents the replication of HCV host cells, however, it is active against multiple genotypes of HCV.[3] The two combination products that include direct acting hepatitis C antivirals include ledipasvir/sofosbuvir (Harvoni®) and a 4-drug regimen of ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®). Paritaprevir and dasabuvir exert their mechanisms of action in the same was as other agents and inhibit NS3/4A protease and NS5B polymerase, respectively. Ledipasvir and Ombitasvir work along the same line as the other agents, but specifically inhibit HCV non-structural protein NS5A. Ritonavir, when used in Viekira Pak®, is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir along with overall drug exposure; it has no direct effect on the hepatitis C virus.[4-5]

Boceprevir is added to peginterferon alfa and ribavirin after a four week lead-in period with dual therapy alone. It is administered three times daily for either 24, 32 or 44 weeks based on a patient's treatment history and HCV ribonucleic acid (RNA) levels.[1] Simeprevir can be initiated with peginterferon alfa and ribavirin or sofosbuvir and is administered once daily. Simeprevir is taken for 12 weeks regardless of treatment history or HCV RNA levels when used with peginterferon and ribavirin, but may be given for 12 or 24 weeks when used in combination with sofosbuvir, depending on cirrhosis status.[2] Prior to initiating therapy with simeprevir in combination with peginterferon and ribavirin, patients with HCV genotype 1a should be screened for the presence of NS3 Q80K polymorphism that is associated with substantially reduced efficacy of simeprevir combination therapy.[2] Alternative therapy should be considered for patients with HCV genotype 1a infection with the Q80K polymorphism.[2] The safety and efficacy of sofosbuvir have not been established in post-liver transplant patients or those who have previously failed therapy with a treatment regimen that includes HCV nonstructural protein 3/4A protease inhibitors.[3]

Efficacy of these agents have been established in multiple clinical trials.[10-25] Newly published guidelines developed by the American Association for the Study of Liver Diseases, Infectious Diseases Society of America and International Antiviral Society-USA have included all currently available treatments in their recommendations.[26] Generally speaking, combination regimens that include newer direct hepatis C antivirals are preferred over older pegylated interferon-based regimens (including those containing older protease inhibitors) due to a higher sustained virologic response (SVR) rate, improved side effects profile, and reduced pill burden.

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