

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.¹⁻⁹ Daklinza® (daclatasvir) is a once-daily NS5A inhibitor indicated for use with an NS5B polymerase inhibitor Sovaldi® (sofosbuvir) for 12 weeks in the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infection. It is the first Food and Drug Administration (FDA)-approved all-oral regimen for the HCV genotype 3 infection that does not require co-administration of interferon or ribavirin.¹ Technivie® (ombitasvir/paritaprevir/ ritonavir) in combination with ribavirin is the first interferon-free Food and Drug Administration (FDA)-approved drug for the treatment of HCV genotype 4 infection.⁷

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.¹⁰⁻¹² 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.¹¹ These agents act via several different mechanisms of action to exert their therapeutic effect.¹⁻⁹ Daclatasvir (Daklinza) binds to the N-terminus of NS5A, a nonstructural protein encoded by HCV, and inhibits both viral ribonucleic acid (RNA) replication and virion assembly.¹ Simeprevir (Olysio®) works via inhibition of the HCV NS3/4A protease of HCV genotype 1a and 1b, thus preventing replication of HCV host cells.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 combination products that include direct acting hepatitis C antivirals include ledipasvir/sofosbuvir (Harvoni®), ombitasvir/paritaprevir/ritonavir (Technivie®), and ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®), elbasvir/grazoprevir (Zepatier®) and sofosbuvir/velpatasvir (Epclusa®). Grazoprevir and paritaprevir inhibit NS3/4A protease, dasabuvir inhibits NS5B polymerase and elbasvir, ledipasvir, ombitasvir and velpatasvir specifically inhibit HCV non-structural protein NS5A. Ritonavir, when used in Technivie® and 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.⁴⁻⁸ Specific indications for each of the direct acting hepatitis C antiviral agents are listed in Table 1.

Efficacy of these agents have been established in multiple clinical trials with numerous clinical trials still underway.¹³⁻⁴⁷ Generally, therapy is determined by clinical guidelines developed by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America and International Antiviral Society (IDSA) rather than the FDA-approved labels of these agents.⁴⁸ The newer combination regimens that include direct hepatitis 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. Each of the direct HCV antivirals is recommended as part of at least one first-line regimen.⁴⁸⁻⁵⁰ Currently, there are no generic direct-acting antivirals available.

Table 1. Current Medications Available in Therapeutic Class¹⁻⁸

Generic (Trade Name)	FDA Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Daclatasvir (Daklinza®)	Treatment of chronic HCV genotype 3 infection in adults as part of a combination antiviral regimen	Tablet: 30 mg 60 mg	-
Simeprevir (Olysio®)	Treatment of chronic HCV genotype 1,4	Capsule: 150	-

Generic (Trade Name)	FDA Approved Indications	Dosage Form/Strength	Generic Availability
	infection in adults as part of a combination antiviral regimen	mg	
Sofosbuvir (Sovaldi®)	Treatment of chronic HCV genotype 1, 2, 3, and 4 infection in adults as part of a combination antiviral regimen	Tablet: 400 mg	-
Combination Products			
Elbasvir/grazoprevir (Zepatier®)	Treatment of chronic HCV genotype 1 and 4 infection in adults as part of a combination antiviral regimen	Tablet: 50/100 mg	-
Ledipasvir/sofosbuvir (Harvoni®)	Treatment of chronic HCV genotype 1, 4, 5, and 6 infection in adults as part of a combination antiviral regimen	Tablet: 90/400 mg	-
Ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®)	Treatment of chronic HCV genotype 1 infection in adults as part of a combination antiviral regimen	Tablet (dasabuvir): 250 mg Tablet (ombitasvir/paritaprevir/ritonavir): 12.5/75/50 mg	-
Ombitasvir/paritaprevir/ritonavir (Technivie®)	Treatment of chronic HCV genotype 4 infection in adults as part of a combination antiviral regimen	Tablet: 12.5/75/50 mg	-
Sofosbuvir/velpatasvir (Epclusa®)	Treatment of chronic HCV genotypes 1, 2, 3, 4, 5 or 6 in adults	Tablet: 400 mg/100 mg	-

FDA=Food and drug administration, HCV=hepatitis C virus

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the direct acting hepatitis C antivirals in various genotypes and regimens.¹³⁻⁴⁷ Overall, data from clinical trials support the FDA-approved indications and dosing recommendations for these agents.
- The FDA approval of daclatasvir was based on the results of ALLY-3, an open-label study evaluating 12 week regimen of daclatasvir 60 mg plus sofosbuvir 400 mg in treatment-naïve and treatment-experienced patients with chronic HCV genotype 3 infection. The primary endpoint was the SVR at post treatment week 12 (SVR12). High SVR12 rates were observed among patients without cirrhosis: 97% (73/75) and 94% (32/34) in treatment-naïve and treatment-experienced patients, respectively. In contrast, SVR12 rates in cirrhotic patients were much lower: 58% (11/19) and 69% (9/13) in treatment-naïve and treatment-experienced patients, respectively.³³
 - An ongoing randomized phase III study is evaluating a combination of daclatasvir, sofosbuvir and ribavirin for 12 or 16 weeks to determine whether the addition of ribavirin or extending treatment duration improved SVR rates in cirrhotic patients with HCV genotype 3 infection.³⁴
- The efficacy of simeprevir 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.^{2,27}
 - 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).^{13,31,32}
 - 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.^{13,31,32}
 - 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.¹³
 - The FDA approval of elbasvir/grazoprevir was based on two placebo-controlled trials and four uncontrolled phase II and III clinical trials in 1,401 patients with genotype HCV genotype 1, 4, or 6 chronic HCV with compensated liver disease (C-EDGE TN, C-EDGE COINFECTION, C-SURFER, C-SCAPE, C-EDGE TE, and C-SALVAGE). All clinical trials evaluated SVR12 as the primary endpoint. Elbasvir/grazoprevir was administered once daily in all trials and ribavirin, if received, was dosed by weight.^{4,14-20}
 - After 12 weeks to therapy, SVR12 rates in C-EDGE TN were 91.7% (genotype 1a), 98.5% (genotype 1b), 100% (genotype 4), and 80% (genotype 6). SVR12 was achieved in 97.1% of cirrhotic patients and 93.9% (231/246) of noncirrhotic patients.¹⁴ After 12 weeks to therapy, SVR12 rates in C-EDGE COINFECTION (HIV-coinfection) were 96.5% (genotype 1a), 95.5% (genotype 1b), 96.4% (genotype 4), and 100% (genotype 6) with 100% of cirrhotic patients. All 35 patients with cirrhosis achieved SVR12.¹⁵ The SVR12 rate after 12 weeks of therapy in C-SURFER (chronic kidney disease) was 99.1%.¹⁶ The overall SVR12 rate in C-SALVAGE (genotype 1, previously failed ≥4 weeks of peginterferon alfa and ribavirin combined with a protease inhibitor [boceprevir, telaprevir, or simeprevir]) was 96.2% overall, including 91.2% in patients with baseline NS3 resistance, and 94.1% (32/34) in cirrhotic patients.^{17,18} C-WORTHY (N=471) was a phase II, randomized, parallel-group, multicenter, open-label study comparing grazoprevir plus elbasvir with or without ribavirin in different patient populations (20 arms total) with chronic HCV genotype 1 infection. SVR12 rates ranged from 80% to 100%.^{19,20}
 - 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.^{20,21,25}
 - 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.^{21,22,26}
 - All studies showed that ledipasvir/sofosbuvir significantly improved SVR12 rate compared to control.^{21,22,26}
 - The FDA approval of ombitasvir/paritaprevir/ritonavir and dasabuvir 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.^{23-25,28,29}
 - 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).^{23-25,28,29}

- Overall, SVR12 rates were high and significantly improved compared with control after 12 weeks of therapy.^{23-25,28,29} 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).²⁵
- The FDA-approval of ombitasvir/paritaprevir/ritonavir in the treatment of HCV genotype 4 was based on the results of an open-label, randomized, multicenter phase IIb PEARL-I study, which evaluated ombitasvir/paritaprevir/ritonavir with or without ribavirin and no cirrhosis. Patients were either treatment-naïve or treatment experienced (prior failure of peginterferon alfa and ribavirin). In treatment-naïve patients, the SVR12s were 100% (42/42) in the ribavirin-containing regimen and 90.9% (40/44) in the ribavirin-free regimen. In the treatment-naïve group without ribavirin, on-treatment virologic breakthrough was reported in one patient (2%), two patients (5%) experienced post-treatment relapse, and one patient (2%) was lost to follow-up. All 49 treatment-experienced patients in the ribavirin-containing group achieved SVR12.³⁵
 - AGATE-I is an ongoing phase III study evaluating ombitasvir/paritaprevir/ritonavir with ribavirin for 12, 16 or 24 weeks in cirrhotic patients with HCV genotype 4 infection, including treatment-naïve patients and those who have failed peginterferon alfa and ribavirin or sofosbuvir-containing regimens.³⁶
 - TURQUOISE-CPB is another ongoing phase III study evaluating ombitasvir/paritaprevir/ritonavir with ribavirin for 24 weeks in patients with HCV genotype 4 infection and decompensated cirrhosis.³⁷
 - Several other studies are planned or recruiting patients to evaluate ombitasvir/paritaprevir/ritonavir with or without ribavirin in less well studied subpopulations with HCV genotype 4 infection, including severe renal disease, children (three to 17 years old), and status post successful treatment of early stage hepatocellular carcinoma.³⁸⁻⁴¹
- The FDA-approval of sofosbuvir/velpatasvir was based on the results of four phase III studies (ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4) in patients with HCV genotype 1 through 6.
 - ASTRAL-1 (N=706) was a phase III, randomized, double-blind, placebo-controlled study evaluating sofosbuvir/velpatasvir 400 mg/100 mg once daily for 12 weeks in adult patients with chronic HCV genotype 1, 2, 4, 5, or 6 infection. Overall, SVR12 rate in the sofosbuvir/velpatasvir group of 99% (618/624) was higher than the prespecified benchmark rate of 85% (P<0.001).⁴²
 - ASTRAL-2 (N=266) and ASTRAL-3 (N=552) were two phase III, randomized, open-label studies comparing sofosbuvir/velpatasvir 400 mg/100 mg once daily for 12 weeks to sofosbuvir 400 mg plus weight-based ribavirin for 12 weeks (ASTRAL-2) or 24 weeks (ASTRAL-3) in adult patients with chronic HCV genotype 2 and HCV genotype 3 infections, respectively. Among patients with HCV genotype 2, the overall SVR12 rate in the 12-week sofosbuvir/velpatasvir group was 99% (133/134) as compared to 94% (124/132) in the 12-week sofosbuvir/ribavirin (P=0.02). Among patients with HCV genotype 3, the overall SVR12 rate in the 12-week sofosbuvir/velpatasvir group was 95% (264/277) as compared to 80% (221/275) in the 24-week sofosbuvir/ribavirin group (P<0.001).⁴³
 - ASTRAL-4 (N=267) was a phase III, randomized, open-label study evaluating sofosbuvir/velpatasvir 400 mg/100 mg once daily for 12 weeks (with or without ribavirin) or 24 weeks in adult patients with chronic HCV genotype 1, 2, 4, or 6 infection and decompensated cirrhosis (Child-Turcotte-Pugh class B). Overall SVR12 rates were 83% (75/90), 94% (82/87), and 86% (77/90) among patients who received sofosbuvir/velpatasvir for 12 weeks, sofosbuvir/velpatasvir and ribavirin for 12 weeks, and sofosbuvir/velpatasvir for 24 weeks, respectively.⁴⁴
 - Other trials are ongoing and full results have not been published. Sofosbuvir/velpatasvir has been evaluated in treating HCV/HIV coinfection in patients with genotypes 1 through 4 (ASTRAL-5), in patients with genotypes 1 through 3 and previous sofosbuvir/velpatasvir failures and in patients undergoing liver transplant.⁴⁵⁻⁴⁷

Key Points within the Medication Class

- 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 guideline.⁴⁸

- 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.
- Each of the new HCV direct acting antivirals are recommended as part of a first-line regimen for at least one genotype and/or patient population.⁴⁸
- 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, five regimens with similar efficacy are recommended. Duration and addition of ribavirin depend on cirrhosis status and/or previous treatment failures.
 - Daclatasvir 60 mg daily (QD) + sofosbuvir 400 mg QD ± ribavirin for 12 to 24 weeks
 - Ledipasvir/sofosbuvir 90/400 mg QD ± ribavirin for 12 to 24 weeks
 - Ombitasvir/ paritaprevir/ritonavir 25/150/100 mg QD + dasabuvir 250 mg twice-daily (BID) ± ribavirin for 12 to 24 weeks
 - Sofosbuvir 400 mg QD + simeprevir 150 mg QD for 12 to 24 weeks
 - Elbasvir/grazoprevir 50/100 mg QD ± ribavirin for 12 to 16 weeks
 - Sofosbuvir/velpatasvir 400 mg/100mg QD for 12 weeks
 - For genotype 2:
 - Daclatasvir 60 mg QD + sofosbuvir (400 mg) QD ± ribavirin for 12 to 24 weeks
 - Sofosbuvir/velpatasvir 400 mg/100mg QD ± ribavirin for 12 weeks
 - For genotype 3:
 - Daclatasvir (60 mg) and sofosbuvir (400 mg) ± ribavirin for 12 to 24 weeks
 - Sofosbuvir/velpatasvir 400 mg/100mg QD ± ribavirin for 12 weeks
 - For Genotype 4:
 - Ledipasvir/sofosbuvir 90/400 mg QD ± ribavirin for 12 to 24 weeks
 - Ombitasvir/ paritaprevir/ritonavir 25/150/100 mg+ ribavirin for 12 weeks
 - Elbasvir/grazoprevir 50/100 mg QD ± ribavirin for 12 to 16 weeks
 - Sofosbuvir/velpatasvir 400 mg/100mg QD for 12 weeks
 - Genotype 5 and 6:
 - Ledipasvir/sofosbuvir 90/400 mg QD for 12 weeks
 - Sofosbuvir/velpatasvir 400 mg/100mg QD for 12 weeks
 - In patients that fail a sofosbuvir, daclatasvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir plus dasabuvir, it is recommended to defer therapy if they have minimal liver disease; guidelines do not offer a specific regimen for recipients with extensive liver disease, but recommend resistance-testing. They recommend treatment for at least 24 weeks with ribavirin, if not contraindicated.⁴⁸
- Other Key Facts:
 - There are also disparities between the FDA-approved indications and first-line recommendations according to the AASLD-IDSA guidelines.^{1-8,48}
 - Prior to initiating therapy with simeprevir (in combination with sofosbuvir) in cirrhotic patients with genotype 1a, they should be screened for the presence of NS3 Q80K polymorphism. Alternative therapy should be considered if this polymorphism is present.²
 - When prescribing ombitasvir/paritaprevir/ritonavir or ombitasvir/paritaprevir/ritonavir/dasabuvir, screening for drugs that should not be coadministered is recommended due to many, often severe, drug interactions.^{5,6}
 - Dose of daclatasvir must be adjusted when given with strong CYP3A inhibitors (30 mg QD) and moderate CYP3A inducers (90 mg QD).¹
 - Testing for NS5A-associated resistance is recommended prior to treatment with sofosbuvir, elbasvir/grazoprevir, ledipasvir/sofosbuvir and sofosbuvir/velpatasvir for several patient populations.⁴⁸

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