Hepatitis C virus (HCV) infection is the most common blood-borne disease; approximately 3.2 million Americans and 130 million to 170 million individuals worldwide are infected with HCV.\(^1,2\) Chronic HCV infection has been called a silent epidemic; the disease can remain quiescent for decades before clinically significant symptoms appear.\(^3\) Because many Americans who are currently living with HCV were infected before blood screening testing for HCV was performed, the prevalence of HCV complications is likely to rise as these individuals enter their 50s and 60s.\(^4\)

Research indicates that by 2015, more than 3 million individuals will have HCV infection that has been present for 20 years or more.\(^5\) This will result in a significant increase in the incidence of advanced liver disease, including cirrhosis, decompensated cirrhosis, and liver cancer.\(^5,6\)

In addition to causing substantial morbidity and mortality, HCV is associated with significant financial consequences.\(^7\) A 2000 study estimated that between 2010 and 2019, the direct medical expenditures for HCV-related conditions will reach nearly $11 billion, the cost of morbidity from disability related to decompensated cirrhosis and hepatocellular carcinoma would reach approximately $21 billion, and the societal cost of premature mortality for patients aged <65 years will exceed $54 billion (in 1999 US dollars).\(^7\)

In the early 1990s, single-agent interferon was the standard of care for patients with HCV infection. Single-agent interferon represented a significant therapeutic advancement, because until then there was no treatment available for HCV infection; however, single-agent interferon offered a sustained virologic response (SVR) rate of less than 10% in patients with HCV genotype 1, the most common HCV subtype.\(^8\) Interferon was then used in combination with ribavirin, increasing the SVR rate by another 14% to 22%.\(^9\) In the early 2000s, pegylated forms of interferon dosed once weekly were introduced. The combination of pegylated interferon with ribavirin increased SVR rates to more than 50% in patients with HCV genotype 1.\(^9,10\) However, HCV genotype 1 was less responsive than HCV genotype 2 and genotype 3.\(^9,10\) Because of this variability in HCV response, low response rates in common HCV subpopulations (ie, black patients, patients with cirrhosis), and side effects associated with interferon and ribavirin, there remained a need to develop novel antiviral therapies.\(^8\)

The treatment options for patients with HCV have evolved significantly in the past few years. HCV is currently the only chronic viral infection that can be cured with antiviral therapy.\(^9\) Although the prevention of infection should be the primary goal of treatment for HCV, no HCV vaccine is available. Therefore, the goals of current anti-HCV approaches are to cure infection, to prevent complications, and to prevent the spread of this disease to other individuals.\(^8\)

In 2011, 2 first-generation protease inhibitors, telaprevir (Incivek) and boceprevir (Victrelis), also known as direct-acting antiviral drugs, were approved by the US Food and Drug Administration (FDA) for HCV genotype infection; both agents offer significant efficacy as measured by the SVR rates.\(^11,12\)

In December 2013, the FDA approved sofosbuvir (Sovaldi) in combination with ribavirin—the first interferon-free, all-oral regimen—for the treatment of patients with HCV genotype 2 and genotype 3. In addition, sofosbuvir in combination with interferon and ribavirin is approved for the treatment of patients with HCV genotype 1 and genotype 4.\(^13,14\) Candidates for sofosbuvir therapy include patients with hepatocellular carcinoma who meet Milan criteria (ie, awaiting liver transplantation) and patients with HCV/human immunodeficiency virus 1 coinfection.\(^13,14\) In contrast to older combination regimens, sofosbuvir regimens require less treatment time: 12 weeks for patients with HCV genotype 1, genotype 2, and genotype 4; and 24 weeks for patients with HCV genotype 3.\(^14\)

Interest and investment in novel therapies for HCV remain strong in light of the increasing incidence of HCV (and its costly complications), unmet patient needs, and the identification of new drug targets through clinical research and discovery.\(^15\) Efforts continue, with the goals of improving the pharmacokinetics and the...
tolerability of these agents, as well as determining treatment strategies—interferon-containing and interferon-free (all oral) regimens—that optimize outcomes.16

**First Combination Tablet for Chronic Hepatitis C Genotype 1 Infection**

On October 10, 2014, the FDA approved the fixed-dose combination capsule of ledipasvir plus sofosbuvir (Harvoni; Gilead Sciences) for the treatment of patients with chronic HCV genotype 1 infection.17,18 Ledipasvir plus sofosbuvir is the first combination tablet approved for the treatment of patients with chronic HCV genotype 1 infection, as well as the first approved regimen that does not require the use of interferon or ribavirin.17 Ledipasvir and sofosbuvir interfere with the enzymes that HCV needs to be able to multiply.17

Ledipasvir was a new agent that was approved for use in combination with sofosbuvir.17,18 Ledipasvir plus sofosbuvir combination therapy was reviewed under the FDA’s priority review program, which expedites the review of drugs that treat serious conditions and that, if approved, would provide significant improvement in the safety or efficacy of the treatment.17

“With the development and approval of new treatments for hepatitis C virus, we are changing the treatment paradigm for Americans living with the disease,” said Edward Cox, MD, MPH, Director of the Office of Antimicrobial Products in the FDA’s Center for Drug Evaluation and Research.17 “Until last year, the only available treatments for hepatitis C virus required administration with interferon and ribavirin. Now, patients and health care professionals have multiple treatment options, including a combination pill to help simplify treatment regimens.”17

**Mechanism of Action**

The combination pill contains a fixed-dose of ledipasvir and sofosbuvir, 2 direct-acting antiviral agents against HCV.15 Ledipasvir is an inhibitor of the NS5A protein, which is required for HCV replication. Sofosbuvir inhibits the HCV NS5B RNA-dependent RNA polymerase, which is also required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form a pharmacologically active triphosphate that can incorporate into the HCV RNA.18

**Dosing and Administration**

The 2-drug, fixed-dose combination contains 90 mg of ledipasvir and 400 mg of sofosbuvir in a single tablet.18 The recommended dosage is 1 tablet taken orally once daily with or without food. Table 1 describes the recommended treatment durations for the specific subsets of patients with HCV genotype 1 infection.18

**Clinical Trials**

The efficacy of ledipasvir-sofosbuvir combination therapy was evaluated in 3 clinical trials that enrolled patients with HCV genotype 1, including patients with or without cirrhosis.18-20 In each clinical trial, patients were randomly assigned to receive ledipasvir-sofosbuvir with or without ribavirin. The primary end point of the studies was the SVR rate, defined as the inability to detect HCV in the blood at least 12 weeks after finishing treatment, indicating that HCV infection has been cured.17,18 The 3 trials are:

- **Study ION-1**: 865 treatment-naïve patients with or without cirrhosis.
- **Study ION-2**: 440 treatment-experienced patients with or without cirrhosis who failed previous therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor.
- **Study ION-3**: 647 treatment-naïve patients without cirrhosis.

**ION-1 Clinical Trial (Study 0102): Treatment- Naïve Adults with or without Cirrhosis**

ION-1 enrolled 865 treatment-naïve patients with genotype 1 HCV, regardless of cirrhosis status.18,19 This randomized study was designed to evaluate 12 weeks and 24 weeks of treatment with ledipasvir-sofosbuvir, used with or without ribavirin.18,19 The patients were randomized to receive 1 of 4 treatment regimens: ledipasvir-sofosbuvir for 12 weeks, ledipasvir-sofosbuvir plus ribavirin for 12 weeks, ledipasvir-sofosbuvir for 24 weeks, or ledipasvir-sofosbuvir plus ribavirin for 24 weeks.18,19 The patients were stratified based on the presence or absence of cirrhosis and on their HCV genotype (1a vs 1b).18

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**Table 1**

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Recommended treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve with or without cirrhosis</td>
<td>12 weeks*</td>
</tr>
<tr>
<td>Treatment-experienced with cirrhosis</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Treatment-experienced with cirrhosis</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

*Ledipasvir/sofosbuvir for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pretreatment HCV RNA <6 million IU/mL.
†Treatment-experienced patients whose disease has failed treatment with peginterferon alfa plus ribavirin or with an HCV protease inhibitor plus peginterferon alfa plus ribavirin. HCV indicates hepatitis C virus.

Source: Harvoni (ledipasvir and sofosbuvir) tablets prescribing information; October 2014.
In ION-1, the demographics and the baseline characteristics were balanced among the treatment groups.\textsuperscript{18} The patients' median age was 54 years (range, 18-80 years), and 59% of patients were male. Overall, 85% of patients were white, 12% were black, and 12% were Hispanic or Latino.\textsuperscript{18} The patients’ mean body mass index (BMI) was 27 kg/m\textsuperscript{2} (range, 18-48 kg/m\textsuperscript{2}). The majority of patients had baseline HCV RNA levels $\geq 800,000$ IU/mL (79%), genotype 1a HCV infection (67%), and non-C/C IL28B alleles (70%). Overall, 16% of patients had cirrhosis.\textsuperscript{18}

The SVR rates for the 12-week treatment groups in the ION-1 clinical trial are summarized in Table 2. Ribavirin did not increase the response rates with ledipasvir-sofosbuvir.\textsuperscript{18}

Virologic failure was rare in the ION-1 patient population, occurring in 0.3% of 865 patients.\textsuperscript{19} No clinical or virologic predictors of virologic failure were identified in these patients, with the exception of suspected nonadherence to therapy.\textsuperscript{19}

ION-2 Clinical Trial (Study 0109): Previously Treated Adults with or without Cirrhosis

In ION-2, a randomized, open-label clinical trial, investigators evaluated 12 weeks and 24 weeks of treatment with ledipasvir-sofosbuvir, with or without ribavirin.\textsuperscript{18} The study included 440 patients with HCV genotype 1 and with or without cirrhosis whose disease did not respond to previous therapy with an interferon-based treatment regimen, including treatment regimens that contained an HCV protease inhibitor. Patients were randomized to 1 of 4 treatment regimens: ledipasvir-sofosbuvir for 12 weeks, ledipasvir-sofosbuvir plus ribavirin for 12 weeks, ledipasvir-sofosbuvir for 24 weeks, or ledipasvir-sofosbuvir plus ribavirin for 24 weeks. Patients were stratified based on the presence or the absence of cirrhosis, HCV genotype (1a vs 1b), and the response to previous HCV therapy (ie, relapse or breakthrough vs nonresponse).\textsuperscript{18}

The demographics and the baseline characteristics were balanced among the treatment groups.\textsuperscript{18} The patients’ median age was 57 years (range, 24-75 years), and 65% of patients were male. Overall, 81% of patients were white, 18% were black, and 9% were Hispanic or Latino.\textsuperscript{18} The patients’ mean BMI was 28 kg/m\textsuperscript{2} (range, 19-50 kg/m\textsuperscript{2}). The majority of patients had baseline HCV RNA levels $\geq 800,000$ IU/mL (89%), genotype 1a HCV infection (79%), and non-C/C IL28B alleles (88%); in addition, 20% of patients had cirrhosis.\textsuperscript{18}

Overall, there were 47% of patients whose disease did not respond to previous therapy with pegylated interferon plus ribavirin.\textsuperscript{18} In addition, there were 53% of patients whose disease failed previous therapy with pegylated interferon plus ribavirin and a protease inhibitor.\textsuperscript{18}

<table>
<thead>
<tr>
<th>Table 2</th>
<th>ION-1 Clinical Trial: Response Rates After 12 Weeks of Treatment in Treatment-Naïve Patients with Chronic HCV Genotype 1 with or without Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>Ledipasvir/sofosbuvir 12 weeks, % (n/N)</td>
</tr>
<tr>
<td>SVR\textsuperscript{a}</td>
<td>99 (210/213)</td>
</tr>
<tr>
<td>SVR by genotype\textsuperscript{b}</td>
<td></td>
</tr>
<tr>
<td>Genotype 1a</td>
<td>98 (142/145)</td>
</tr>
<tr>
<td>Genotype 1b</td>
<td>100 (67/67)</td>
</tr>
<tr>
<td>SVR by cirrhosis\textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>99 (176/177)</td>
</tr>
<tr>
<td>Yes</td>
<td>94 (32/34)</td>
</tr>
</tbody>
</table>
| \textsuperscript{a}Excluding 1 patient with genotype 4 infection. 
\textsuperscript{b}One patient without a confirmed subtype for genotype 1 infection and 1 patient with genotype 4 infection were excluded from this subgroup analysis. 
\textsuperscript{c}Patients with missing cirrhosis status were excluded from this subgroup analysis. |

HCV indicates hepatitis C virus; SVR, sustained virologic response. 
Source: Harvoni (ledipasvir and sofosbuvir) tablets prescribing information; October 2014.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>ION-2 Trial: Response Rates at 12 and 24 Weeks of Treatment in Treatment-Experienced Patients with Chronic HCV Genotype 1 and with or without Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>Ledipasvir/sofosbuvir 12 weeks, % (n/N)</td>
</tr>
<tr>
<td>SVR</td>
<td>94 (102/109)</td>
</tr>
<tr>
<td>SVR by genotype</td>
<td></td>
</tr>
<tr>
<td>Genotype 1a</td>
<td>95 (82/86)</td>
</tr>
<tr>
<td>Genotype 1b</td>
<td>87 (20/23)</td>
</tr>
<tr>
<td>SVR by cirrhosis\textsuperscript{a}</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>95 (83/87)</td>
</tr>
<tr>
<td>Yes</td>
<td>86 (19/22)</td>
</tr>
<tr>
<td>SVR by previous HCV therapy</td>
<td></td>
</tr>
<tr>
<td>Pegylated interferon + ribavirin</td>
<td>93 (40/43)</td>
</tr>
<tr>
<td>HCV protease inhibitor + pegylated interferon + ribavirin</td>
<td>94 (62/66)</td>
</tr>
<tr>
<td>SVR by response to previous HCV therapy</td>
<td></td>
</tr>
<tr>
<td>Relapse or breakthrough</td>
<td>95 (57/60)</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>92 (45/49)</td>
</tr>
</tbody>
</table>
| \textsuperscript{a}Patients with missing cirrhosis status were excluded from this subgroup analysis. 
HCV indicates hepatitis C virus; SVR, sustained virologic response. 
Source: Harvoni (ledipasvir and sofosbuvir) tablets prescribing information; October 2014. |
The SVR rates for the treatment groups in the ION-2 clinical trial are summarized in Table 3. Ribavirin did not increase the response rates with ledipasvir-sofosbuvir.18

ION-3 Clinical Trial (Study 0108): Treatment-Naïve Adults without Cirrhosis

ION-3, a randomized, open-label clinical trial, was conducted in 647 treatment-naïve patients with HCV genotype 1 and without cirrhosis.18,20 Patients were stratified by the HCV genotype (1a vs 1b) and were randomized to 1 of 3 treatment groups: ledipasvir-sofosbuvir for 8 weeks, ledipasvir-sofosbuvir for 12 weeks, or ledipasvir-sofosbuvir plus ribavirin for 8 weeks.18,20

The demographics and the baseline characteristics were balanced among the treatment groups.18 The patients’ median age was 55 years (range, 20-75 years), and 58% of the patients were male. Overall, 78% of patients were white, 19% were black, and 6% were Hispanic or Latino. The patients’ mean BMI was 28 kg/m² (range, 18-56 kg/m²). In addition, 81% of patients had baseline HCV RNA levels ≥800,000 IU/mL, 80% had genotype 1a HCV infection, and 73% had non-C/C IL28B alleles.18

In all 3 treatment groups, the SVR rates were significantly higher than the adjusted historical control rate of 60% (P <.001).19,20 Ribavirin was not shown to increase the response rates with ledipasvir-sofosbuvir.19,20 The SVR rates after 8 weeks and 12 weeks of treatment with ledipasvir-sofosbuvir are summarized in Table 4.

The SVR rates in patients with characteristics that are historically associated with a poor response to interferon-based treatment, such as high viral load at baseline, black race, and HCV genotype 1a infection, were similar to patients without these characteristics.20

The treatment difference between the 8-week and 12-week course of ledipasvir-sofosbuvir was 2.3% (97.5% confidence interval, 7.2% to 2.5%).18 Among patients with a lower baseline HCV RNA (ie, <6 million IU/mL), the SVR rate was 97% with 8 weeks of treatment and 96% with 12 weeks of treatment with ledipasvir-sofosbuvir.18

Safety

The safety assessment of ledipasvir-sofosbuvir was based on the pooled data from the 3 phase 3 clinical trials of patients with HCV genotype 1 with compensated liver disease (with or without cirrhosis). These 3 studies evaluated ledipasvir-sofosbuvir combination therapy for 8 weeks, 12 weeks, or 24 weeks and included 215 patients, 539 patients, and 326 patients, respectively.18

Adverse reactions that occurred in ≥10% of patients who received ledipasvir-sofosbuvir (8 weeks, 12 weeks, or 24 weeks) were fatigue and headache.18 Nausea, diarrhea, and insomnia were also reported at rates between 5% and 10%; the majority of these adverse reactions were categorized as grade 1.18

The percentage of patients who permanently discontinued 8 weeks, 12 weeks, or 24 weeks of ledipasvir-sofosbuvir treatment as a result of adverse events was 0%, <1%, and 1%, respectively. Ledipasvir-sofosbuvir has no contraindications.18

Warnings and Precautions

Reduced therapeutic effect with P-glycoprotein inducers. The use of ledipasvir-sofosbuvir together with P-glycoprotein inducers, such as rifabutin and St. John’s wort, may significantly decrease plasma concentrations of ledipasvir and sofosbuvir, potentially reducing the combination’s therapeutic effect; therefore, the use of ledipasvir-sofosbuvir with P-glycoprotein inducers is not recommended.18

Related drugs. Ledipasvir-sofosbuvir combination therapy should not be used with other drugs that contain sofosbuvir.18

Specific Populations

Pregnancy. Ledipasvir-sofosbuvir is listed as pregnancy category B.18 No adequate studies with ledipasvir-sofosbuvir were conducted in pregnant women. Ledipasvir-sofosbuvir should only be used during pregnancy if the potential benefits justify the potential risk to the fetus.18

Nursing mothers. It is not known whether ledipasvir-sofosbuvir combination therapy and its metabolites are present in human breast milk.18 The developmental and the health benefits of breastfeeding, as well as the mother’s clinical need for ledipasvir-sofosbuvir and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition, should be considered.18
**Pediatric use.** The safety and efficacy of ledipasvir-sofosbuvir have not been established in pediatric patients.18

**Geriatric use.** The clinical trials of ledipasvir-sofosbuvir included 117 patients aged ≥65 years.18 No overall differences in safety or efficacy were observed between older and younger patients. Dose adjustment of ledipasvir-sofosbuvir is not recommended for geriatric patients.18

**Renal impairment.** Patients with mild or moderate renal impairment do not require dosage adjustment of ledipasvir-sofosbuvir. Because the combination drug's safety and efficacy have not been established in patients with severe renal impairment or end-stage renal disease requiring hemodialysis, no dosage adjustment for ledipasvir-sofosbuvir can be recommended.18

**Hepatic impairment.** No dosage adjustment of ledipasvir-sofosbuvir is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C). The safety and efficacy have not been established in patients with decompensated cirrhosis.18

**Conclusion**

Once-daily ledipasvir-sofosbuvir combination therapy is a highly active and safe oral option for patients with HCV genotype 1 infection. As the first combination pill approved for the treatment of this patient population, ledipasvir-sofosbuvir combination therapy represents a significant therapeutic advancement for the treatment of patients with HCV genotype 1 infection.

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**References**


