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Formulary Drug Reviews

Sofosbuvir

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Generic Name:	Sofosbuvir
Proprietary Name:	*Sovaldi* (Gilead Sciences)
Approval Rating:	1
Therapeutic Class:	Antiviral Agents
Similar Drugs:	Boceprevir, Simeprevir, Telaprevir
Sound- or Look-Alike Names:	None

INDICATIONS

Sofosbuvir is indicated for the treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen. Sofosbuvir in combination with ribavirin and/or peginterferon alfa has shown efficacy in subjects with hepatitis C virus (HCV) genotype 1, 2, 3, or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 coinfection. Sofosbuvir is not indicated for use as monotherapy for any of these HCV genotypes. Patients infected with HCV genotype 1 or 4 should be treated with a combination of sofosbuvir, peginterferon alfa, and ribavirin for 12 weeks. In select cases, patients infected with genotype 1 HCV who are unable to tolerate interferon or who are interferon ineligible can be treated with sofosbuvir plus ribavirin for 24 weeks. Patients infected with HCV genotype 2 should be treated with sofosbuvir plus ribavirin for 12 weeks. Patients infected with HCV genotype 3 should be treated with sofosbuvir plus ribavirin for 24 weeks. Those patients with hepatocellular carcinoma awaiting liver transplantation should be treated with sofosbuvir plus ribavirin for up to 48 weeks or until liver transplantation, whichever occurs first.[1] See **Table 1** for a comparison of the US Food and Drug Administration (FDA)–approved indications for HCV antiviral agents.

Sofosbuvir is also being evaluated in combination with GS-5885 with or without ribavirin, with GS-0938, with ledipasvir with or without ribavirin, with daclatasvir with or without ribavirin, and with simeprevir with or without ribavirin for the treatment of various HCV genotypes and in combination

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Table 1. Comparison of FDA-approved indications for hepatitis C antiviral agents[1,16-18]

	Sofosbuvir	Boceprevir	Simeprevir	Telaprevir
Brand name	*Sovaldi*	*Victrelis*	*Olysio*	*Incivek*
Manufacturer	Gilead Sciences	Merck	Janssen	Vertex Pharmaceuticals
Approval date	December 6, 2013	May 13, 2011	November 22, 2013	May 23, 2011
Indication	Treatment of chronic hepatitis C as a component of a combination antiviral treatment regimen; efficacy established in subjects with HCV genotype 1, 2, 3, or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 coinfection	Chronic HCV genotype 1 infection in adult patients with compensated liver disease, including cirrhosis, who are treatment naive or who have failed previous therapy with interferon and ribavirin, including prior null responders, partial responders, and relapsers	Chronic HCV genotype 1 infection in adult patients with compensated liver disease, including cirrhosis[a]	Chronic HCV genotype 1 infection in adult patients with compensated liver disease, including cirrhosis, who are treatment naive or who have failed previous therapy with interferon-based treatment, including prior null responders, partial responders, and relapsers

Note: HCV = hepatitis C virus; HIV = human immunodeficiency virus.
[a]Simeprevir has been studied in treatment-naive patients and patients who have failed previous therapy with peginterferon and ribavirin, and the US Food and Drug Administration (FDA)-approved labeling contains dosing recommendations for patients who are treatment naive or who have failed previous therapy with interferon and ribavirin, including prior null responders, partial responders, and relapsers, although these populations are not specified in the indication.

with daclatasvir in a liver transplant recipient with severe recurrent cholestatic hepatitis C.[2–8]

In 2013, it was estimated that 3.2 million patients in the United States had a chronic HCV infection, but only 1.8 million (50%) have been diagnosed and 1 to 1.2 million (32% to 38%) have been referred for care. Of these patients, only 7% to 11% were treated, and a successful outcome was achieved in 170,000 to 200,000 (5% to 6%) of the 3.2 million with HCV infection.[9] The problem with the current treatment of HCV infections is that interferon is needed as part of the drug regimen. This forces patients to use an injectable drug that is not well tolerated. The development of a new drug regimen that does not require the use of an interferon will be an important advance in the treatment of HCV infections.[10–15]

CLINICAL PHARMACOLOGY

Sofosbuvir is a prodrug with an active metabolite that has direct-acting antiviral activity that inhibits HCV NS5B RNA–dependent polymerase, a vital component in viral replication. The active metabolite of sofosbuvir, uridine analog triphosphate (GS-461203), has activity against genotypes 1, 2, 3, 4, and 6 by acting as a chain terminator.[1,11,19–23] GS-461203 may also show efficacy against genotype 5a. GS-461203 does not inhibit human DNA polymerase or human or mitochondrial RNA polymerase.[1]

Use of sofosbuvir in combination with interferon alpha or ribavirin did not show antagonistic effects of HCV RNA reduction. In vitro, reduced susceptibility of sofosbuvir has been noted with HCV genotypes 1a, 2a, 2b, 3a, 4a, 5a, and 6a. This change in susceptibility can be mainly attributed to the NS5B substitution S282T with several genotypes also containing the M289L substitution. The NS5B substitution S282T has also shown reduced susceptibility to GS-461203. Although the clinical significance is unknown, observations of L159F, V321A, S282T, C316N, and L320F substitutions in patients with genotypes 1a, 1b, 2b, and 3a were noted in clinical trials. Several genotype 3a infections with L159F and V321A substitutions did not demonstrate altered susceptibility to sofosbuvir. Conversely, genotype 1a, 1b, and 2b patients (some with hepatocellular carcinoma awaiting liver transplant) with 282T, L159F, C316N, or L320F substitutions noted reduced susceptibility to sofosbuvir.[1]

Sofosbuvir was noted to have activity against HCV resistant to NS3/4A protease inhibitors, NS5A inhibitors, and NS5B nonnucleoside inhibitors; HCV expressing ribavirin-associated T390I and F415Y substitutions was susceptible to sofosbuvir. HCV that expressed the sofosbuvir-associated substitution S282T was noted to be susceptible to NS5A inhibitors and ribavirin.[1]

PHARMACOKINETICS

Peak plasma concentrations were noted at 0.5 to 2 hours after oral administration.[1] Peak plasma concentration of the inactive GS-331007 metabolite occurred between 2 and 4 hours.[1,19] The mean steady-state area under the curve (AUC_{0-24}) in genotypes 1 to 6 HCV-infected patients concurrently treated with ribavirin with or without peginterferon was 828 and 6,790 ng•h/mL for sofosbuvir and GS-331007, respectively. In healthy patients given sofosbuvir alone, the AUC_{0-24} of sofosbuvir was 39% higher and the AUC_{0-24} of GS-331007 was 39% lower compared with HCV-infected patients. A dose-proportional relationship was noted in sofosbuvir and GS-331007 AUCs (dose range, 200 to 1,400 mg). Sofosbuvir can be taken without regard to food; administration after a high-fat meal did not alter the AUC, maximal drug concentration (C_{max}), or exposure of GS-331007 compared with fasting states.[1]

Sofosbuvir undergoes approximately 61% to 65% binding to plasma protein that is independent of drug concentrations between 1 and 20 mcg/mL. In contrast, GS-331007 exhibits minimal protein binding.[1]

Sofosbuvir is extensively metabolized in the liver through a variety of mechanisms. This metabolic process requires human cathepsin A (CatA) or carboxylesterase 1 (CES1) to catalyze the hydrolysis of the carboxyl ester moiety. Additionally, the histidine triad nucleotide-binding protein 1 (HINT-1) facilitates phosphoramidate cleavage and the pyrimidine nucleotide biosynthesis pathway facilitating phosphorylation. This process yields an active nucleoside analogue triphosphate of sofosbuvir, GS-461203. The dephosphorylation of GS-461203 leads to production of GS-331007, a metabolite that has no anti-HCV activity in vitro. Sofosbuvir accounts for 4% and GS-331007 accounts for 90% of drug-related material systemic exposure.[1]

Sofosbuvir is mainly cleared through the renal pathway, with 80% of a 400 mg dose recovered in the urine. Most (78%) of the drug recovered in the urine was GS-331007, while sofosbuvir accounted for 3.5%. Less prominent pathways of sofosbuvir elimination are through the feces (14%) and expired air (2.5%). The median terminal half-life of sofosbuvir is 0.4 hours, with a median terminal half-life of 27 hours for GS-331007.[1]

When compared with subjects having an estimated glomerular filtration rate (eGFR) greater than 80 mL/min/1.73 m^2, AUCs for sofosbuvir and GS-331007 increased with increasing renal impairment (from mild and moderate to severe renal failure). A hemodialysis period of 4 hours removed approximately 18% of a given dose. No dosing adjustment is required for patients with mild and moderate renal impairment; however, no dose recommendation can be made for patients with severe impairment or for those requiring dialysis. In comparison with patients within the normal hepatic function range, AUCs for both sofosbuvir and GS-331007 increased. Cirrhosis did not have any clinically relevant effects. Dosing adjustments are not required for patients with mild, moderate, or severe hepatic impairment. Ethnic background, gender, and age did not appear to have clinically relevant effects on sofosbuvir pharmacokinetics, and changes associated with sofosbuvir pharmacokinetics in pediatric patients have not been determined.[1]

COMPARATIVE EFFICACY:

Indication: Chronic Hepatitis C Virus Infection

Guidelines

Guideline: An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Disease

Reference: Ghany MG, et al, 2011[24]

Comments: Treatment-naive patients should be started on boceprevir or telaprevir in combination with peginterferon alfa and ribavirin. Neither drug should be used without peginterferon and weight-based ribavirin. Treatment-experienced patients should be re-treated with boceprevir or telaprevir in combination with peginterferon alfa and weight-based ribavirin if patients had virological relapse or were partial responders to previous treatment. Re-treatment with telaprevir in combination with peginterferon alfa and weight-based ribavirin is recommended for patients classified as null responders to a course of standard interferon alfa or peginterferon alfa and/or weight-based ribavirin. Response-guided therapy of treatment-experienced patients using a boceprevir- or telaprevir-based regimen can be recommended for patients who have relapsed, can be considered for patients who had partial response, and cannot be recommended for null responders. If patients continue to have detectable HCV RNA greater than 100 units at week 12 with boceprevir-based regimens and detectable HCV RNA greater than 1,000 units at week 4 or 12 with telaprevir-based regimens, treat-

ment should be withdrawn to prevent the development of antiviral resistance.

Guideline: Update on the management and treatment of hepatitis C virus infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office
Reference: Yee HS, et al, 2012[25]
Comments: Treatment-naive patients with genotype 1 infection should be started on boceprevir or telaprevir in combination with peginterferon alfa and ribavirin. If telaprevir is used in a treatment-naive noncirrhotic patient and the patient achieves extended rapid virologic response at week 12, the telaprevir component of the triple-drug regimen can be discontinued and the patient continued on peginterferon alfa plus ribavirin for an additional 12 weeks. If HCV RNA is detectable but is less than 1,000 units/mL at week 4 and remains less than 1,000 units/mL or becomes undetectable by week 12, the telaprevir component of the triple-drug regimen can be discontinued and the patient continued on peginterferon alfa plus ribavirin for an additional 36 weeks. If a telaprevir-containing regimen is used in treatment-naive cirrhotic patients who achieve HCV RNA that is undetectable or less than 1,000 units/mL at treatment weeks 4 and 12, telaprevir should be discontinued at week 12 and peginterferon alfa plus ribavirin continued for another 36 weeks.

In treatment-naive noncirrhotic patients receiving a boceprevir-containing regimen, if HCV RNA declines by at least $\log_{10}$ during the 4-week lead-in and HCV RNA is undetectable at weeks 8 to 24, boceprevir plus peginterferon alfa and ribavirin for 24 weeks is sufficient. If HCV RNA is detectable at week 8 but less than 100 units/mL at week 12 and negative at week 24, boceprevir plus peginterferon alfa and ribavirin should be continued until week 36, followed by peginterferon alfa and ribavirin alone for 12 more weeks. If HCV RNA declines by less than 1 $\log_{10}$ during the lead-in, boceprevir plus peginterferon alfa and ribavirin can be continued for 44 weeks. If a boceprevir-containing regimen is used in treatment-naive cirrhotic patients, 44 weeks of boceprevir plus peginterferon alfa and ribavirin therapy is required after the 4-week lead-in.

For patients who previously failed peginterferon alfa plus ribavirin therapy, re-treatment with boceprevir or ribavirin and peginterferon alfa plus ribavirin may be considered, particularly in patients who relapse. The guidelines also provide recommendations regarding various re-treatment situations.

Studies

Drug: Sofosbuvir plus Pegylated Interferon Alfa-2a and Ribavirin
Reference: Kowdley KV, et al, 2013 (ATOMIC study)[26]
Study Design: Randomized, open-label, multicenter phase 2 study
Study Funding: Gilead Sciences
Patients: 316 patients with HCV genotype 1, 11 patients with HCV genotype 4, and 5 patients with HCV genotype 6. All patients were 18 years and older and were treatment-naive for HCV infection.
Intervention: Patients were randomized to treatment with sofosbuvir 400 mg once daily plus peginterferon alfa-2a and ribavirin for 12 weeks (cohort A), sofosbuvir 400 mg once daily plus peginterferon alfa-2a and ribavirin for 24 weeks (cohort B), or sofosbuvir 400 mg once daily plus peginterferon alfa-2a and ribavirin for 12 weeks followed by either sofosbuvir monotherapy or sofosbuvir plus ribavirin for 12 weeks (cohort C).
Results
Primary Endpoint(s)

- Sustained virological response posttreatment at week 24 (SVR24) in the intent-to-treat population:
  - Patients with HCV genotype 1: SVR24 was 89% (95% confidence interval [CI], 77% to 96%) in cohort A, 89% (95% CI, 82% to 94%) in cohort B, and 87% (95% CI, 81% to 92%) in cohort C. No difference in response rate was noted when cohort A was compared with cohort B (P = .94) and when cohort A was compared with cohort C (P = .78).
  - Patients with HCV genotype 4: SVR24 was 82%.
  - All 5 patients with HCV genotype 6 achieved SVR24.

Secondary Endpoint(s)

- Relapse occurred in only 7 patients, and all of these had genotype 1 infections.

Comments: The majority of patients in this study were infected with HCV genotype 1. The number of patients with HCV genotype 4 and genotype 6

was very small. The ATOMIC study was designed primarily to determine whether a shorter treatment period (12 weeks) with the triple-drug regimen was possible.

Drug: Sofosbuvir plus Ribavirin vs Sofosbuvir plus Peginterferon Alfa and Ribavirin
Reference: Gane EJ, et al, 2013 (ELECTRON trial)[27]
Study Design: Randomized, open-label, phase 2a study
Study Funding: Pharmasset & Gilead Sciences
Patients: 95 patients with chronic HCV genotype 1, 2, or 3 infection without cirrhosis. The majority of patients were White (approximately 80%), with an approximate age of 47 years.
Intervention: Patients with HCV genotype 2 or 3 infection were randomly assigned in a 1:1:1:1 ratio to 1 of 4 treatment groups. All patients received oral sofosbuvir 400 mg once daily plus weight-based ribavirin for 12 weeks. Group 1 received only the sofosbuvir and ribavirin combination therapy. Groups 2, 3, and 4 also received peginterferon alfa-2a 180 mcg subcutaneously for 4, 8, and 12 weeks, respectively. The protocol was amended to include 2 additional groups of previously untreated patients with HCV genotype 2 or 3 infection: 10 patients were treated for 12 weeks with sofosbuvir monotherapy and 10 patients were treated with sofosbuvir plus peginterferon alfa-2a and ribavirin for 8 weeks. The study also treated 35 patients with HCV genotype 1 infection: 25 treatment-naive patients and 10 patients who did not respond to prior treatment with peginterferon and ribavirin for at least 12 weeks.
Results
Primary Endpoint(s)
- Sustained viral response (SVR):
  - All 40 patients (100%) with HCV genotype 2 or 3 treated with sofosbuvir plus ribavirin had undetectable levels of serum HCV RNA at 2, 4, 8, 12, 24, and 48 weeks after treatment.
  - All 10 patients (100%) treated with sofosbuvir plus peginterferon alfa-2a and ribavirin for 8 weeks had SVR at 12 weeks after treatment (all 9 patients for whom data were available had SVR at 24 weeks after treatment).
  - Sofosbuvir monotherapy achieved SVR at 12 and 24 weeks after treatment in 6 of 10 (60%) patients. Relapse occurred in 4 patients; 2 had HCV genotype 3 infections and detectable levels of HCV RNA at 2 weeks after treatment, and 2 had HCV genotype 2 infection and detectable levels of HCV RNA at 4 weeks after treatment.
  - 25 patients were treatment naive with HCV genotype 1 infection; 21 (84%) had SVR at 24 weeks after treatment, and 4 (16%) experienced relapse during follow-up.
  - 10 patients with HCV genotype 1 infection who did not respond to prior treatment were also treated; only 1 (10%) had SVR at 24 weeks after treatment with sofosbuvir plus ribavirin.

Limitations: The study included a small number of patients from 2 medical centers in New Zealand.

Drug: Sofosbuvir plus Peginterferon Alfa and Ribavirin
Reference: Lawitz E, et al, 2013 (NEUTRINO trial)[28]
Study Design: Single-group, open-label study
Study Funding: Gilead Sciences
Patients: 327 treatment-naive patients with HCV genotype 1, 4, 5, or 6 infection. HCV genotype 1 presented in 89%, genotype 4 in 9%, and genotype 5 or 6 in 2%. The majority of the population was White, and 17% had cirrhosis.
Intervention: Sofosbuvir 400 mg orally (PO) once daily, weight-based ribavirin (1,000 mg daily in patients with a body weight of less than 75 kg, and 1,200 mg daily in patients with a body weight of at least 75 kg) PO in divided doses, and peginterferon alfa-2a 180 mcg subcutaneously once weekly.
Results
Primary Endpoint(s)
- Sustained virological response posttreatment at week 12 (SVR12): 90% (95% CI, 87% to 93%) had SVR with HCV genotypes 1, 4, 5, and 6 with sofosbuvir plus peginterferon and ribavirin compared with an adjusted historical response rate of 60% ($P < .001$).

Secondary Endpoint(s)
- Rate of response did not vary greatly based on HCV genotype: 89% with HCV genotype 1 and 96% with genotype 4.
- Rate of SVR12 was 92% (95% CI, 89% to 95%) among patients without cirrhosis and 80% (95% CI, 67% to 89%) with cirrhosis.

Comments: The results of the FISSION and NEUTRINO studies were reported in a single paper

published in the *New England Journal of Medicine*. The NEUTRINO study enrolled treatment-naive patients with HCV genotypes 1, 4, 5, and 6 infection treated with sofosbuvir plus peginterferon alfa and ribavirin. There was no comparator group. The study was conducted in multiple centers in the United States.

Drug: Sofosbuvir plus Ribavirin vs Peginterferon alfa plus Ribavirin
Reference: Lawitz E, et al, 2013 (FISSION trial)[28]
Study Design: Randomized, open-label, active-control noninferiority study
Study Funding: Gilead Sciences
Patients: 499 patients with HCV genotype 2 or 3 infection. Cirrhosis presented in 20% of the sofosbuvir group and 21% of the peginterferon group.
Intervention: Randomized (1:1) to either 12 weeks of sofosbuvir plus weight-based ribavirin or 24 weeks of peginterferon alfa-2a plus ribavirin. The sofosbuvir group received sofosbuvir 400 mg PO once daily and weight-based ribavirin (1,000 mg daily in patients with a body weight of less than 75 kg, and 1,200 mg daily in patients with a body weight of at least 75 kg) PO in divided doses. The peginterferon alfa plus ribavirin group received peginterferon alfa 180 mcg subcutaneously once weekly and oral ribavirin 800 mg daily in 2 divided doses.
Results
Primary Endpoint(s)
- SVR12: Noninferiority, both groups had a 67% SVR. The absolute difference between the 2 groups after adjustment for stratification factors was 0.3% (95% CI, –7.5% to +8%).

Secondary Endpoint(s)
- SVR based on genotype was 97% with genotype 2 and 56% with genotype 3 in the sofosbuvir plus ribavirin group and was 78% and 63%, respectively, in the peginterferon plus ribavirin group.
- Patients with cirrhosis achieving SVR: 47% of those treated with sofosbuvir plus ribavirin and 38% of those treated with peginterferon plus ribavirin.

Comments: The results of the FISSION and NEUTRINO studies were reported in a single paper published in the *New England Journal of Medicine*. The FISSION study was a multicenter study conducted in the United States, Australia, New Zealand, Italy, Sweden, and the Netherlands.

Drug: Sofosbuvir plus Ribavirin vs Placebo
Reference: Jacobson IM, et al, 2013 (POSITRON study)[29]
Study Design: Randomized, multicenter, international phase 3 study
Study Funding: Gilead Sciences
Patients: 278 patients with HCV genotype 2 or 3 infection who previously discontinued interferon therapy owing to unacceptable adverse reactions, who had a concurrent medical condition precluding therapy with an interferon-containing regimen, or who decided against treatment with an interferon-containing regimen. Study used a 3:1 randomization, with stratification based on presence or absence of cirrhosis. Approximately 20% of the study population had evidence of compensated cirrhosis. Mean age was 52 years in both groups, and the majority was White (approximately 92%). HCV genotype 2 infection was detected in 53% of the treatment group and 48% of the control group. HCV genotype 3 infection was detected in 47% and 52%, respectively.
Intervention: Sofosbuvir 400 mg PO once daily and weight-based ribavirin (1,000 mg daily in patients with a body weight of less than 75 kg and 1,200 mg daily in patients with a body weight of at least 75 kg) PO twice daily for 12 weeks.
Results
Primary Endpoint(s)
- SVR12: 78% (95% CI, 72% to 83%) in the treatment group and 0% in the placebo group ($P < .001$).

Secondary Endpoint(s)
- No virologic relapse after week 12 in responders in the treatment group.
- SVR was the same at 12 and 24 weeks in the treatment group.
- SVR12 based on HCV genotype:
  - 93% of patients with HCV genotype 2 in the treatment group.
  - 61% of patients with HCV genotype 3 in the treatment group.
- Impact of cirrhosis
  - Patients without cirrhosis had SVR12 of 81% (92% with HCV genotype 2 and 68% with HCV genotype 3).
  - Patients with cirrhosis had SVR12 of 61% (94% with HCV genotype 2 and 21% with HCV genotype 3).

Comments: The results of the POSITRON and FUSION studies were reported in a single paper published in the *New England Journal of Medicine*. The POSITRON study enrolled a group of patients for whom interferon therapy was not an option. A small number of these patients had a poor response to previous treatment; 3% were nonresponsive and 6% relapsed in the placebo group, and 1% were nonresponsive and 5% relapsed in the treatment group.

Reference: Jacobson IM, et al, 2013 (FUSION study)[29]
Study Design: Randomized, multicenter, international phase 3 study
Study Funding: Gilead Sciences
Patients: 201 patients with HCV genotype 2 or 3 infection who did not respond to prior treatment with an interferon-containing regimen. The study used a 1:1 randomization, with stratification based on presence or absence of cirrhosis and HCV genotype 2 or 3 infection. Approximately 30% of the study population had evidence of compensated cirrhosis. Mean age was 54 years in both groups, and most were White (approximately 86%). HCV genotype 2 infection was detected in 35% of the 12-week treatment group and in 33% of the 15-week treatment group; HCV genotype 3 infection was detected in 62% and 64%, respectively. Response to previous treatment (prior to study enrollment) was classified as "nonresponse" in 24% of the 12-week group and 26% of the 16-week group, and as "relapse" in 76% of the 12-week group and 74% in the 16-week group.
Intervention: Sofosbuvir 400 mg PO once daily and weight-based ribavirin (1,000 mg daily in patients with a body weight of less than 75 kg, and 1,200 mg daily in patients with a body weight of at least 75 kg) PO twice daily for either 12 weeks followed by 4 weeks of matching placebo or 16 weeks of sofosbuvir plus ribavirin.
Results
Primary Endpoint(s)

- Sustained virological response posttreatment at week 16 (SVR16):
  - Historical control rate was 25%.
  - SVR16 was 50% (95% CI, 40% to 60%) in the 12-week group and 75% in the 16-week group ($P < .001$ for each comparison).
  - –23% difference between the 2 active treatments (95% CI, –35% to –11%; $P < .001$).

Secondary Endpoint(s)

- SVR16 based on HCV genotype:
  - HCV genotype 2: 86% with 12 weeks and 94% with 16 weeks (–8% difference; 95% CI, –24% to +9).
  - HCV genotype 3: 30% with 12 weeks and 62% with 16 weeks (–32% difference; 95% CI, –48% to –15%).
- Impact of cirrhosis:
  - 12 weeks of therapy:
    - Patients without cirrhosis had SVR16 of 61% (96% with HCV genotype 2 and 37% with HCV genotype 3).
    - Patients with cirrhosis had SVR16 of 31% (60% with HCV genotype 2 and 19% with HCV genotype 3).
  - 16 weeks of therapy:
    - Patients without cirrhosis had SVR16 of 76% (100% with HCV genotype 2 and 63% with HCV genotype 3).
    - Patients with cirrhosis had SVR16 of 66% (78% with HCV genotype 2 and 61% with HCV genotype 3).

Comments: The results of the POSITRON and FUSION studies were reported in a single paper published in the *New England Journal of Medicine*. The FUSION study enrolled a group of patients who did not respond to prior treatment with an interferon-containing regimen. The number needed to treat for SVR between the 2 active treatments was 4.35 for the 16-week treatment period.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Sofosbuvir requires combined treatment with peginterferon alfa, ribavirin, or both agents; contraindications to these agents, if used, apply to sofosbuvir drug regimens. Refer to the prescribing information for each product for further information regarding specific contraindications.[1]

The ribavirin component used in sofosbuvir combination therapy is associated with the risk of birth defects and fetal death. Therefore, sofosbuvir treatment regimens requiring ribavirin are contraindicated in women who are pregnant or may become pregnant, or in men whose female partners are pregnant.[1]

Warnings and Precautions

Potent inducers of P-glycoprotein (P-gp), including rifampin and St. John's wort, should be avoided during sofosbuvir therapy. Concurrent use of these

agents may cause reduced plasma concentration of sofosbuvir and potentially reduce therapeutic effects.[1]

Both ribavirin and interferon alfa are classified as Pregnancy Category X. Warnings and precautions associated with sofosbuvir therapy may be more related to the peginterferon alfa and ribavirin components of the drug regimen. Appropriate measures should be taken to prevent pregnancy in female patients or female partners of male patients receiving sofosbuvir combination regimens that include ribavirin or interferon. Ribavirin may have teratogenic effects or lead to death in an exposed fetus, and interferon may have abortifacient effects. In animal models, available evidence demonstrates teratogenic and embryocidal effects with ribavirin and abortifacient effects with interferon. Immediately prior to starting therapy with ribavirin, patients should present with a negative pregnancy test, and testing should recur at monthly intervals throughout therapy and for 6 months after treatment conclusion. When using ribavirin or interferon in combination with sofosbuvir, women of childbearing potential and their male partners must use 2 nonhormonal forms of contraception during treatment and for 6 months after treatment completion. No data are available on the effectiveness of systemic hormonal contraceptives in patients taking sofosbuvir. Health care providers and patients should be encouraged to report drug exposure during pregnancy to the Ribavirin Pregnancy Registry (1-800-593-2214), which monitors maternal-fetal outcomes.[1] Patients coinfected with HCV/HIV-1 who are taking antiretrovirals should contact the Antiretroviral Pregnancy Registry (1-800-258-4263).

Sofosbuvir is classified as Pregnancy Category B; there is little evidence regarding the safety of sofosbuvir in pregnant women. In animal models (rats and rabbits), effects on fetal development were not observed at AUCs from 5- to 10-fold to 12- to 28-fold above recommended doses in humans.[1]

The extent of sofosbuvir excretion and its metabolites in human breast milk is unknown. In animal models, the predominate metabolite GS-331007 was found in the milk of lactating rats, without effect on the offspring. Benefits and risks of sofosbuvir therapy should be considered when determining whether to continue ribavirin in a breast-feeding woman because of the potential for adverse reactions. Refer to the ribavirin prescribing information for more detailed information.[1]

The safety and efficacy of sofosbuvir in children younger than 18 years have not been established.[1]

In reviewing exposure of sofosbuvir in 90 subjects 65 years and older, similar response rates to younger subjects were observed.[1]

Sofosbuvir dosage adjustment in patients with mild or moderate renal impairment is not required. However, safety and efficacy have not been evaluated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or end-stage renal disease (ESRD) requiring hemodialysis. Patients with an estimated creatinine clearance less than 50 mL/min may require dosage adjustment with ribavirin and peginterferon alfa. Refer to the prescribing information for these products for more detailed information.[1]

Sofosbuvir dosage adjustment in patients with mild, moderate, or severe hepatic impairment (defined as Child-Pugh class A, B, or C, respectively) is not required. Safety and efficacy have not been evaluated in patients with decompensated cirrhosis. Peginterferon alfa is contraindicated in liver decompensation; refer to the prescribing information for more detailed information.[1]

Safety data from 223 HCV/HIV-1 coinfected patients appear similar to observations in HCV monoinfected patients. Grade 3 or 4 elevations in total bilirubin were observed in 30 of 32 patients (94%) receiving concurrent atazanavir and 2 patients (1.5%) not taking atazanavir. None of the patients concurrently taking atazanavir noticed an increase in transaminase levels.[1]

Use of sofosbuvir for prevention of posttransplant HCV reinfection in hepatocellular carcinoma patients waiting for liver transplant has been evaluated in an open-label clinical trial. The primary study outcome was posttransplant virologic response, which referred to an HCV RNA level less than the lower limit of quantification at the 12-week time point. Enrolled subjects were diagnosed with hepatocellular carcinoma and met Milan criteria. The treatment regimen included sofosbuvir 400 mg in combination with weight-based ribavirin daily for 24 to 48 weeks or until time of liver transplant. At the time of interim analysis, 45 of the 61 evaluated patients were classified as genotype 1, 44 patients had a baseline Child-Pugh-Turcotte (CPT) score less than 7, and all patients had baseline unadjusted Model for End-Stage Liver Disease (MELD) scores equal to or less than 14. Additionally, 37 patients had an HCV RNA less than the lower limit of quantification, and 41 patients completed 48 weeks of treatment prior to transplant. In 36 patients reaching the 12-week time point, 23 of 36 (64%) achieved a posttransplant viro-

logic response, and the safety data regarding treatment prior to transplant were similar to phase 3 clinical trials.[1]

Safety and efficacy of sofosbuvir in post–liver transplant patients have not been established.[1]

There are insufficient data to provide dosing for patients with genotype 5 or 6 HCV infections.[1]

ADVERSE REACTIONS

The most commonly reported adverse reactions associated with sofosbuvir-containing therapies in clinical trials included fatigue, nausea, headache, insomnia, pruritus, anemia, irritability, cough, diarrhea, rash, and arthralgia.[1,27–29] Treatment-emergent adverse reactions occurring in 15% or more of subjects in any treatment arm are shown in **Table 2**. Adverse events that occurred in less than 1% of patients during clinical trials were hematologic- and psychiatric-type reactions. These reported events included pancytopenia and severe depression that included both suicidal ideation and suicide.[1]

Several laboratory abnormalities noted with sofosbuvir-containing regimens included changes to hemoglobin, neutrophils, platelets, bilirubin, creatine kinase, and lipase. The changes in hematologic parameters are shown in **Table 3**. Bilirubin increased more than 2.5 times the upper limit of normal (ULN) but returned to baseline by posttreatment week 4 in 0% of patients receiving sofosbuvir and ribavirin for 12 weeks, 1% of patients receiving peginterferon alfa and ribavirin for 24 weeks, and 3% of patients receiving sofosbuvir and ribavirin for 12 or 24 weeks. Asymptomatic creatine kinase elevations equal to or greater than 10 times the ULN occurred in less than 1% of patients receiving peginterferon alfa and ribavirin for 24 weeks, 1% of patients receiving sofosbuvir with peginterferon alfa and ribavirin for 12 weeks, and 2% of patients receiving sofosbuvir and ribavirin for 12 weeks. Asymptomatic elevations in lipase greater than 3 times the ULN were seen in less than 1% of patients given sofosbuvir with peginterferon alfa and ribavirin for 12 weeks, 2% of patients given sofosbuvir and ribavirin for 12 weeks, 2% of patients given sofosbuvir and ribavirin for 24 weeks, and 2% of patients given peginterferon alfa and ribavirin for 24 weeks.[1]

Discontinuation of treatment due to adverse events occurred in 4% of patients receiving placebo, 1% of patients receiving sofosbuvir and ribavirin for 12 weeks, less than 1% of patients receiving sofosbuvir and ribavirin for 24 weeks, 11% of patients receiving peginterferon alfa and ribavirin for 24 weeks, and 2% of patients receiving sofosbuvir, peginterferon alfa, and ribavirin for 12 weeks.[1] The most common adverse reactions leading to discontinuation of therapy were anemia and neutropenia, which were both attributed to the peginterferon or ribavirin therapy.[26,28,29]

DRUG INTERACTIONS

Drugs that are potent inducers of P-gp in the intestine, such as St. John's wort and rifampin, should be avoided with sofosbuvir due to the potential for reduced plasma concentrations and therapeutic effects. The metabolite of sofosbuvir, GS-331007, accounts for a majority (90%) of systemic drug-related material exposure. Despite metabolic activation of sofosbuvir through low affinity and high-capacity hydrolase and nucleotide phosphorylation paths, concurrent drugs are unlikely to be affected. Although sofosbuvir is a substrate for P-gp and breast cancer resistance protein (BCRP), GS-331007 is not.[1]

Inhibitors of P-gp or BCRP may be given concomitantly with sofosbuvir, because they may increase sofosbuvir concentration without increases in GS-331007 concentrations. Sofosbuvir and GS-331007 are not expected to inhibit P-gp or BCRP and therefore are not expected to increase exposures of drugs that are substrates of these transporters.[1] **Table 4** is a list of potential drug interactions with sofosbuvir.

There is no pharmacokinetic drug–drug interaction between sofosbuvir and GS-5885 (inhibitor of NS5A protein), GS-9669 (NS5B Thumb II polymerase inhibitor), rilpivirine/darunavir/ritonavir, raltegravir, cyclosporine A, or tacrolimus.[30–32] GS-5885 and GS-9669 are in clinical development for the treatment of HCV infections and may be combined with sofosbuvir.[30] In clinical trials evaluating drug interactions with sofosbuvir, no dose adjustment was required in either drug for the following: cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, methadone, raltegravir, rilpivirine, tacrolimus, or tenofovir disoproxil fumarate.[1]

RECOMMENDED MONITORING

No specific recommendations for HCV RNA monitoring are provided in the prescribing information.[1] However, recommended monitoring may include periodic complete blood counts and platelet counts because of the concurrent use of ribavirin and/or interferon alfa.

Table 2. Treatment-emergent adverse reactions occurring in ≥15% of subjects in any treatment arm[1]

Adverse event	Regimens without interferon			Regimens containing interferon	
	Placebo (12 weeks) (*n* = 71)	Sofosbuvir plus ribavirin[a] (12 weeks) (*n* = 650)	Sofosbuvir plus ribavirin[a] (24 weeks) (*n* = 250)	Peginterferon alfa plus ribavirin[b] (24 weeks) (*n* = 243)	Sofosbuvir plus peginterferon alfa and ribavirin (12 weeks) (*n* = 327)
Fatigue	24%	38%	30%	55%	59%
Headache	20%	24%	30%	44%	36%
Nausea	18%	22%	13%	29%	34%
Insomnia	4%	15%	16%	29%	25%
Pruritus	8%	11%	27%	17%	17%
Anemia	0%	10%	6%	12%	21%
Asthenia	3%	6%	21%	3%	5%
Rash	8%	8%	9%	18%	18%
Decreased appetite	10%	6%	6%	18%	18%
Chills	1%	2%	2%	18%	17%
Influenza-like illness	3%	3%	6%	18%	16%
Pyrexia	0%	4%	4%	14%	18%
Diarrhea	6%	9%	12%	17%	12%
Neutropenia	0%	< 1%	< 1%	12%	17%
Myalgia	0%	6%	9%	16%	14%
Irritability	1%	10%	10%	16%	13%

[a]Patients received weight-based ribavirin dosing.
[b]Patients received ribavirin 800 mg regardless of weight.

DOSING

The usual sofosbuvir dose is 400 mg PO once daily with or without food and in combination with weight-based ribavirin or interferon alfa plus weight-based ribavirin, depending on the patient's viral genotype (see **Table 5**).[1]

Dosing Adjustments

Genotypes 1 and 4

Ribavirin or peginterferon should be reduced or discontinued (according to the prescribing information for each respective agent) in patients with a severe adverse reaction to these agents.[1]

Genotypes 2 and 3

In patients demonstrating a serious adverse reaction to ribavirin, the dose should be adjusted or discontinued, as appropriate, until the reaction is reduced or resolved. **Table 6** includes suggestions for ribavirin dosing adjustments based on cardiac or hemoglobin status.[1]

Sofosbuvir dose reduction is not recommended and discontinuation is recommended when indicated HCV combination therapies are discontinued.[1] There are no available sofosbuvir dosing recommendations for patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or ESRD. Exposure to the sofosbuvir metabolite is expected to increase up to 20-fold in these patients.[1]

PRODUCT AVAILABILITY

The New Drug Application for sofosbuvir was filed with the FDA in April 2013.[33] Sofosbuvir was approved for marketing in the United States on December 6, 2013.[34] Sofosbuvir is provided in a single 400 mg strength. Each tablet is yellow, capsule-

Table 3. Proportion of subjects reporting changes in hematologic parameters[1]

Hematologic parameter	Regimens free of interferon			Regimens containing interferon	
	Placebo (12 weeks) (*n* = 71)	Sofosbuvir plus ribavirin[a] (12 weeks) (*n* = 647)	Sofosbuvir plus ribavirin[a] (24 weeks) (*n* = 250)	Peginterferon alfa plus ribavirin[b] (24 weeks) (*n* = 242)	Sofosbuvir plus peginterferon alfa and ribavirin (12 weeks) (*n* = 327)
Hemoglobin					
< 10 g/dL	0%	8%	6%	14%	23%
< 8.5 g/dL	0%	1%	< 1%	2%	2%
Neutrophils					
≥ 0.5 to < 0.75 x 10^9/L	1%	< 1%	0%	12%	15%
< 0.5 x 10^9/L	0%	< 1%	0%	2%	5%
Platelets					
≥ 25 to < 50 x 10^9/L	3%	< 1%	1%	7%	< 1%
< 25 x 10^9/L	0%	0%	0%	0%	0%

[a]Patients received weight-based ribavirin dosing.
[b]Patients received ribavirin 800 mg regardless of weight.

Table 4. Potential drug interactions with sofosbuvir that may warrant dose or regimen adjustment[a1]

Concurrent medication	Drug interaction	Commentary
Anticonvulsant		
Carbamazepine Phenytoin Phenobarbital Oxcarbazepine	Decreased sofosbuvir and GS-331007 plasma concentrations	Coadministration is not recommended.
Antimycobacterial		
Rifabutin Rifampin Rifapentine	Decreased sofosbuvir and GS-331007 plasma concentrations	Coadministration is not recommended. Note that sofosbuvir should be avoided with rifampin.
Herbal products		
Hypericum perforatum (St. John's wort)	Decreased sofosbuvir and GS-331007 plasma concentrations	Coadministration should be avoided.
HIV protease inhibitor		
Tipranavir/ritonavir	Decreased sofosbuvir and GS-331007 plasma concentrations	Coadministration is not recommended.

[a]Interactions based on predictions or drug interaction studies.

shaped, and film-coated in appearance, with a "GSI" imprint on one side and "7977" on the other side.[1]

Sofosbuvir is available in bottles containing 28 tablets. It should be ensured that sofosbuvir is only dispensed in the original container and kept at room temperature below 30°C (86°F). Sofosbuvir should not be dispensed if the seal at the bottle opening is broken or missing.[1]

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

A REMS program is not required for marketing sofosbuvir.[34]

CONCLUSION

Sofosbuvir is a new drug for the treatment of HCV. Sofosbuvir offers the benefit of oral adminis-

Table 5. Treatment regimens for sofosbuvir combination therapy[1]

Monoinfected HCV or HCV/HIV-1 coinfections	Treatment regimen	Duration
Genotype 1 or 4 chronic hepatitis C	Sofosbuvir with peginterferon alfa[a] and ribavirin[a,b]	12 weeks[c]
Genotype 2 chronic hepatitis C	Sofosbuvir and ribavirin[a,b]	12 weeks
Genotype 3 chronic hepatitis C	Sofosbuvir and ribavirin[a,b]	24 weeks
Hepatocellular carcinoma awaiting liver transplant	Sofosbuvir and ribavirin[a,b]	48 weeks or up to time of liver transplant

[a]For complete information, refer to the prescribing information of each respective agent.
[b]Based on weight; patients weighing < 5 kg should receive 1,000 mg and patients weighing ≥75 kg should receive 1,200 mg. Both regimens are to be taken with food and in 2 divided doses. The dose should be reduced in patients with creatinine clearance ≤50 mL/min.
[c]After consideration of risks versus benefits, patients who are interferon ineligible may consider treatment with sofosbuvir plus ribavirin for 24 weeks.

Table 6. Dose adjustment for coadministered ribavirin[a] based on cardiac or hemoglobin status[1]

Laboratory values	Consider ribavirin dose reduction to 600 mg/day	Consider discontinuation[b]
Hemoglobin in patients without cardiac disease	< 10 g/dL	< 8.5 g/dL
Hemoglobin in patients with a history of stable cardiac disease	Decreased hemoglobin ≥ 2 g/dL in any 4-wk treatment period	< 12 g/dL despite 4 wk of dose reduction

[a]For complete information, refer to the ribavirin prescribing information.
[b]After ribavirin is stopped due to laboratory or clinical reasons, an attempt can be made to restart it at 600 mg titrated to 800 mg; ribavirin should not be restarted at the higher recommended starting doses (1,000 or 1,200 mg).

tration, is well tolerated, and requires a shorter treatment course than other drugs. Sofosbuvir is for use in combination with ribavirin for genotypes 2 or 3 HCV-infected patients and with ribavirin and pegylated interferon alfa for genotype 1 HCV-infected patients. Although a study sponsored by Gilead Sciences and using sofosbuvir plus ribavirin is only currently being conducted in patients with genotypes 1 and 3 HCV,[35] the current prescribing information suggests that patients intolerant of pegylated interferon alfa may use sofosbuvir with ribavirin for a total duration of 24 weeks.

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