



CDEC FINAL RECOMMENDATION

SOFOSBUVIR

(Sovaldi — Gilead Sciences Canada, Inc.)

Indication: Chronic Hepatitis C Infection

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that sofosbuvir (SOF) be listed for the treatment of chronic hepatitis C (CHC) virus infection in adult patients with compensated liver disease, including cirrhosis, if the following clinical criteria and conditions are met:

Clinical criteria:

- Patients with genotype 1 CHC infection, in combination with pegylated-interferon and ribavirin (Peg-IFN/RBV):
 - a fibrosis stage of F2, F3, or F4
 - treatment naive.
- Patients with genotype 2 CHC infection, in combination with RBV:
 - a fibrosis stage of F2, F3, or F4
 - previous treatment experience with Peg-IFN/RBV or a medical contraindication to Peg-IFN/RBV.
- Patients with genotype 3 CHC infection, in combination with RBV:
 - a fibrosis stage of F2, F3, or F4
 - previous treatment experience with Peg-IFN/RBV or a medical contraindication to Peg-IFN/RBV.

Conditions:

- Reduced price
- Funding should not exceed a duration of 12 weeks for the treatment of patients with genotype 1 or 2 CHC and 24 weeks for the treatment of patients with genotype 3 CHC.

Reasons for the Recommendation:

1. A single-arm trial (NEUTRINO; N = 327) demonstrated that treatment with SOF + Peg-IFN/RBV achieved high rates of sustained virologic response (SVR) 12 for treatment-naive patients with genotype 1 CHC. In addition, the treatment regimen for SOF has a decreased duration of Peg-IFN/RBV therapy relative to the recommended regimens for other direct-acting antiviral drugs.

2. Four randomized controlled trials (RCTs) (FISSION [N = 499], FUSION [N = 201], POSITRON [N = 280], and VALENCE [N = 419]) demonstrated that treatment with SOF + RBV achieves high rates of SVR 12 for patients with genotype 2 and 3 CHC.
3. At the submitted price (\$██████ per day), CDEC concluded that SOF + Peg-IFN/RBV is likely to be cost-effective for genotype 1 CHC patients who are treatment-naïve and genotype 2 CHC patients who are treatment experienced with Peg-IFN/RBV or have a medical contraindication to Peg-IFN/RBV. However, SOF + RBV treatment may not be cost-effective for some patients with genotype 3 CHC; therefore, a reduction in price is required to support a recommendation for use in patients with genotype 3 CHC who are treatment experienced with Peg-IFN/RBV or have a medical contraindication to Peg-IFN/RBV.
4. For all genotypes, treatment of patients with higher levels of fibrosis is more cost-effective.

Background:

SOF is a nucleotide polymerase inhibitor and the first direct-acting antiviral drug against the hepatitis C virus to act at a target other than the protease. SOF is indicated for the treatment of CHC infection in adult patients with compensated liver disease, including cirrhosis, for the treatment of genotype 1 and 4 CHC infection in combination with Peg-IFN/RBV and genotype 2 and 3 CHC infection in combination with RBV.

SOF is available as 400 mg tablets and the product monograph recommends the following dosage regimens:

- genotypes 1 and 4: SOF 400 mg daily + Peg-IFN/RBV for 12 weeks
- genotype 2: SOF 400 mg daily + RBV for 12 weeks
- genotype 3: SOF 400 mg daily + RBV for 16 to 24 weeks.

Summary of CDEC Considerations:

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of SOF, a critique of the manufacturer's pharmaco-economic evaluation, and a summary of patient group-submitted information about outcomes and issues important to individuals living with CHC infection.

Patient Input Information

The following is a summary of information provided by five patient groups that responded to the CDR call for patient input:

- Hepatitis C is a serious and potentially life-threatening liver disease that is contracted through blood-to-blood contact with an infected person.
- Debilitating physical symptoms may develop, such as chronic fatigue, mental confusion, memory loss, and mood swings that can result in job loss and a reliance on disability benefits or social assistance.
- The lives of caregivers and family members are made much more difficult when a loved one has CHC. They often assume greater financial and child-care responsibilities and worry about their own risk of infection. Family break-up is common.
- People living with CHC want early and uncomplicated access to affordable treatments that have tolerable side effects and that cure the disease in patients with all genotypes. They

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also want treatments that are shorter in duration than the current treatment periods and a reduced pill burden. Many are waiting for new IFN-free or RBV-free therapies to avoid the adverse events associated with those drugs.

- Patients who were not cured with other CHC treatments want the opportunity to be treated with SOF.

Clinical Trials

The CDR systematic review included five studies. One single-arm study (NEUTRINO [N = 327]) included patients with genotypes 1, 4, 5 and 6, while the others (FISSION [N = 499], FUSION [N = 201], POSITRON [N = 280], and VALENCE [N = 419]) included patients with genotypes 2 and 3. FISSION was an open-label non-inferiority RCT that compared 12 weeks of SOF + RBV with 24 weeks of Peg-IFN/RBV in a treatment-naïve population. FUSION was a double-blind RCT that compared 12 weeks of SOF + RBV with 16 weeks of SOF + RBV, in patients who had failed prior treatment with Peg-IFN, with or without RBV. POSITRON was a double-blind RCT that compared 12 weeks of SOF + RBV with placebo, in a population of patients who were intolerant, unwilling, or ineligible for Peg-IFN therapy. VALENCE was initially designed as a double-blind RCT comparing 12 weeks of SOF + RBV with placebo in a mixed treatment-naïve and treatment-experienced patient population. After a protocol amendment during the study, the placebo group was halted and the duration of SOF + RBV was extended to 24 weeks for patients with genotype 3, but remained 12 weeks for patients with genotype 2.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- SVR 12 — defined as hepatitis C virus (HCV) ribonucleic acid (RNA) less than the lower limit of quantification (LLOQ) 12 weeks after stopping all study drugs.
- Relapse — defined as having HCV RNA greater than or equal to LLOQ during the post-treatment period having achieved HCV RNA less than LLOQ at the end of treatment, confirmed with two consecutive values or last available post-treatment measurement.
- SF-36 — a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life. SF-36 consists of eight dimensions: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, role limitations due to physical, and role limitations due to emotional problems. SF-36 also provides two component summaries, the physical component summaries (PCS) and the mental component summary (MCS).
- Chronic Liver Disease Questionnaire (CLDQ) — an instrument used to assess the health-related quality of life for patients with chronic liver disease. CLDQ measures activity/energy, emotion, worry, systemic symptoms, and CLDQ total score. All domains and the total score are based on a Likert scale of 0 (worse) to 7 (best).
- FACIT-Fatigue (FACIT-F) scale — a 40-item scale used to assess fatigue and the impact of fatigue on daily activities. Physical, emotional, social and functional well-being domains, as well as a fatigue subscale make up the total score ranging from 0 (worst) to 160 (best).
- Work Productivity and Activity Impairment (WPAI) questionnaire — an instrument used to measure the impact of a disease on work and on daily activities.

The primary outcome of all studies was the proportion of patients with SVR 12. The non-inferiority margin for the primary outcome in FISSION was –15%.

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EfficacyGenotypes 1 and 4

- The proportion of the total patient population in NEUTRINO that achieved SVR 12 (91%) was statistically significantly greater than an external control of 60% ($P < 0.001$). SVR responses were highest with genotypes 4, 5, and 6 (97%), followed by genotype 1a (92%) and 1b (82%). In the overall population, the proportion of SVR 12 responders was 80% in patients with cirrhosis and 93% in patients without cirrhosis.
- The mean (standard deviation [SD]) changes from baseline in the NEUTRINO study for SF-36-PCS (−6.5 [9.8]), SF-36-MCS (−6.9 [10.6]), CLDQ-HCV (−0.6 [1.0]), and FACIT-F (−19.8 [25.1]) were statistically significantly lower (worse) at end of therapy compared with baseline. The WPAI reported a mean (SD) increase in the percentage of overall impairment of 22.1% (31.6) for work and 22.0% (31.3) for activity.

Genotypes 2 and 3

- The proportion of patients with SVR 12 was reported as follows:
 - FISSION: there was a similar proportion of SVR 12 responders in the SOF + RBV and Peg-IFN/RBV groups (67% in each group, with a between-group difference of 0.3% [95% confidence interval [CI], −7.5% to 8.0%]). The criterion for non-inferiority was met; however, superiority of SOF + RBV versus Peg-IFN/RBV was not demonstrated.
 - FUSION: a statistically significantly greater proportion of patients treated with 16 weeks of SOF + RBV had an SVR 12 compared with those treated with 12 weeks of SOF + RBV (73% versus 51%, with a difference in proportions of −22% [95% CI: −34% to 10%], $P < 0.001$).
 - POSITRON: a statistically significantly greater proportion of patients treated with SOF + RBV had an SVR 12 response compared with those in the placebo group (78% versus 0%, difference in proportions of 77% [95% CI: 71% to 84%], $P < 0.001$).
 - VALENCE: the proportion of patients with an SVR 12 was 93% for genotype 2 patients treated for 12 weeks with SOF + RBV and 85% in genotype 3 patients treated for 24 weeks with SOF + RBV. There were no responders in the 85 patients treated with placebo; the proportion of SVR 12 responders in the genotype 3 group treated with 12 weeks of SOF + RBV was 27%.
- The proportion of patients experiencing relapse was reported as follows:
 - FISSION: 30% with SOF + RBV versus 21% with Peg-IFN/RBV (relative risk [RR] 1.40; 95% CI: 1.02 to 1.93), $P = 0.04$.
 - FUSION: 27% in the 16-week SOF + RBV group versus 47% in the 12-week; RR 1.72 (95% CI: 1.16 to 2.53), $P = 0.006$.
 - POSITRON: 21% with SOF + RBV and a placebo-relapse proportion could not be calculated as there were no responders in this group.
 - VALENCE: 7% for genotype 2 patients taking 12 weeks of SOF + RBV and 14% for genotype 3 patients taking 24 weeks of SOF + RBV.
- Changes in SF-36 were reported as follows:
 - FISSION: The mean (SD) change from baseline in the SF-36-PCS was 0.5 (8.7) in the SOF + RBV group and −4.3 (9.3) in the Peg-IFN/RBV group ($P < 0.001$). The mean (SD) change from baseline in the SF-36-MCS was −3.7 (11.5) and −8.1 (12.8) for SOF + RBV and Peg-IFN/RBV ($P = 0.012$).

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- FUSION: there was no statistically significant difference between the 16-week and 12-week SOF + RBV regimens in either the SF-36-PCS ($P = 0.14$) or SF-36-MCS ($P = 0.17$).
- POSITRON: There was no statistically significant difference between SOF + RBV and placebo for changes in the SF-36-PCS ($P = 0.57$) or SF-36-MCS ($P = 0.12$).
- FUSION was the only study to report the CLDQ-HCV, FACIT-F, and WPAI-Hep C; there were no statistically significant differences between treatments in changes from baseline for any of these measures.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one adverse event was reported as follows:
 - NEUTRINO: 95% with SOF + RBV for 12 weeks.
 - FISSION: 86% with SOF + RBV for 12 weeks and 96% with Peg-IFN/RBV.
 - POSITRON: 89% with SOF + RBV and 78% with placebo.
 - FUSION: 89% with SOF + RBV for 12 weeks and 88% with SOF + RBV for 16 weeks.
 - VALENCE: 86% with SOF + RBV for 12 weeks, 91% with SOF + RBV for 24 weeks, and 72% with placebo.
- The proportion of patients who experienced at least one serious adverse event was reported as follows:
 - NEUTRINO: 1% with SOF + RBV for 12 weeks.
 - FISSION: 3% with SOF + RBV and 1% with Peg-IFN/RBV.
 - POSITRON: 5% with SOF + RBV and 2% with placebo.
 - FUSION: 5% with SOF + RBV for 12 weeks and 3% with SOF + RBV for 16 weeks.
 - VALENCE: 0% with SOF + RBV for 12 weeks, 4% with SOF + RBV for 24 weeks, and 2% with placebo.
- The proportion of patients who withdrew from the trials as a result of adverse events was reported as follows:
 - NEUTRINO: 2% with SOF + RBV for 12 weeks.
 - FISSION: 1% with SOF + RBV and 12% with Peg-IFN/RBV.
 - POSITRON: 2% with SOF + RBV and 4% with placebo.
 - FUSION: 1% with SOF + RBV for 12 weeks, < 1% with SOF + RBV for 24 weeks, and 1% with placebo.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis (CUA) conducted over a lifetime horizon. The base-case analysis was comprised of 24 subgroups (genotypes 1, 2, or 3); cirrhosis (presence or absence), and previous treatment exposure (treatment naive, treatment experienced, interferon ineligible, unwilling/intolerant). In genotype 1 treatment-naive patients, SOF + Peg-IFN/RBV for 12 weeks was compared with telaprevir + Peg-IFN/RBV, boceprevir + Peg-IFN/RBV, and Peg-IFN/RBV alone. In genotype 2 patients, SOF + RBV for 12 weeks was compared with Peg-IFN/RBV alone or no treatment. In genotype 3 patients, SOF + RBV for 16 weeks was compared with Peg-IFN/RBV alone or no treatment.

For efficacy data, in genotype 1 patients, in the absence of a comparator group in NEUTRINO, for the base-case analysis, SVR rates were sourced from the intervention group of SPRINT-2 and ADVANCE for telaprevir and boceprevir, and from IDEAL for Peg-IFN/RBV (naive indirect

treatment comparison). In a sensitivity analysis, comparative SVR rates from a manufacturer-funded unpublished network meta-analysis (NMA) in non-cirrhotic patients were used. In genotype 2 and 3 patients, SVR rates with SOF were based on POSITRON (IFN ineligible) and FUSION (treatment experienced), while SVR rates for Peg-IFN/RBV were based on historical controls and SVR rates for no treatment were based on POSITRON (IFN ineligible) or assumed to be 0% (treatment experienced). Frequency of adverse events (anemia, depression, and rash), irrespective of severity, was sourced from clinical trials or product monographs. The cumulative incidence of complications (compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, and death) during a patient's lifetime was forecasted using transition probabilities drawn from the literature. Health state utility values were derived from a Canadian study by Hsu et al. Utility decrement during antiviral therapy and utility increment following SVR were applied. Drug costs for comparators were obtained from the Quebec drug formulary. Costs to manage adverse events were obtained from a study using Quebec administrative databases. Liver disease health state costs were derived from a Canadian study on hepatitis B by Dakin et al.

The manufacturer reported that for all genotypes and subgroups, SOF in combination with Peg-IFN/RBV or RBV alone was economically attractive versus comparators, except in genotype 2 prior non-responders with cirrhosis, genotype 3 IFN ineligible or intolerant patients with cirrhosis, and genotype 3 prior non-responders without cirrhosis.

CDR identified a number of limitations with the manufacturer's analyses:

- The design of NEUTRINO and FUSION required use of historical controls and naive indirect comparisons, which generates uncertainty in the comparative efficacy of SOF with other direct-acting antiviral drugs and Peg-IFN/RBV.
- There was uncertainty in the results of the NMA used by the manufacturer for a sensitivity analysis in genotype 1 non-cirrhotic patients.
- Many of the clinical comparisons were based on small sample sizes and the results in some subgroups were not consistent with the overall findings from FUSION and POSITRON (e.g., patients with cirrhosis presenting better SVR rates than those without cirrhosis).
- The potential longer duration of therapy with SOF in genotype 3 patients (24 weeks instead of 16 weeks) was not considered.

CDR performed additional sensitivity analyses to test the impact of the identified areas of uncertainty considering the following input parameters: Saskatchewan Drug Benefit costs, more conservative SVR estimates, the utility increment assigned to patients who achieved SVR was reduced from 0.08 to 0.07, the time horizon shortened to 80 years of age instead of 100, and a lower cost of anemia.

- In genotype 1 treatment-naive patients without cirrhosis, the cost-effectiveness of SOF versus telaprevir, boceprevir, and Peg-IFN/RBV is uncertain, due to a lack of a direct comparator group in the NEUTRINO trial, and wide credible intervals in the manufacturer's NMA. Using results from the NMA, the incremental cost-utility ratio (ICUR) for SOF versus Peg-IFN/RBV, telaprevir, and boceprevir was \$50,266 per quality-adjusted life-year (QALY), \$11,531 per QALY, and \$14,030 per QALY respectively. Using conservative SVR estimates (lower bound of the 95% credible interval from the NMA for SOF), the ICUR for SOF versus Peg-IFN/RBV was \$135,391 per QALY, and SOF was dominated by telaprevir and boceprevir. In patients with cirrhosis, using the lower bound of the 95% CI for SOF and assuming a 15% higher SVR rate for telaprevir and boceprevir, the ICUR for SOF was

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\$7,119 per QALY versus Peg-IFN/RBV and \$3,237 per QALY versus boceprevir, but was dominated by telaprevir.

- In genotype 2 patients ineligible to receive Peg-IFN/RBV, ICURs for SOF versus no treatment remained under \$30,000, regardless of cirrhosis status (\$28,983 and \$3,268 per QALY respectively). In genotype 2 patients with prior relapse/breakthrough, ICURs for SOF ranged from \$23,944 to \$31,487 per QALY versus no treatment and versus Peg-IFN/RBV, except in patients with cirrhosis where the ICUR was \$62,162 versus Peg-IFN/RBV. In genotype 2 prior non-responders, the ICUR for SOF compared with no treatment or Peg-IFN/RBV were less attractive in patients without cirrhosis (ranging from \$61,564 to \$136,936), and SOF was dominated by Peg-IFN/RBV and no treatment in patients with cirrhosis.
- In genotype 3 patients ineligible to receive Peg-IFN/RBV, ICURs for SOF versus no treatment were above \$75,000 per QALY, regardless of cirrhosis status. In genotype 3 patients with prior relapse/breakthrough, SOF was either dominated or resulted in ICURs > \$150,000 per QALY versus no treatment and versus Peg-IFN/RBV in patients without cirrhosis, but resulted in ICURs below \$31,000 per QALY in patients with cirrhosis. In prior non-responders, compared with no treatment and Peg-IFN/RBV, SOF was either dominated, or had ICURs above \$150,000 per QALY.

At the submitted price of \$ [REDACTED] per day, for genotype 1 patients, the cost of a 12-week course of SOF is \$ [REDACTED], which is more costly than a 12-week course of simeprevir (\$39,605, including wholesaler mark-up as simeprevir was not listed on any participating drug plans at the time of the SOF review) or telaprevir (\$34,968), or a 24-week course of boceprevir (\$25,200), but less costly than a 44-week course of boceprevir (\$46,200).

When considering the cost of treatment regimens for genotype 1 patients (treatments used in combination with Peg-IFN/RBV), SOF (with a 12 week course of Peg-IFN/RBV, \$ [REDACTED] is more costly than simeprevir or telaprevir with a 24-week course of Peg-IFN/RBV (approximately \$49,110 and \$44,470, respectively), as well as a 24-week course of boceprevir with a 28 or 48-week course of Peg-IFN/RBV (approximately \$36,280 and \$44,200, respectively), but less costly than simeprevir or telaprevir regimens with a 48-week course of Peg-IFN/RBV (approximately \$58,610 and \$53,970, respectively), and a 44-week course of boceprevir with a 48-week course of Peg-IFN/RBV (approximately \$65,200).

For genotype 2 patients, the cost of a 12-week course of SOF is \$ [REDACTED], which is more costly than a 24-week or 48-week course of Peg-IFN/RBV (\$9,300 to \$20,500). For genotype 3 patients, the cost of a 16-week or 24-week course of SOF is \$ [REDACTED] or \$ [REDACTED] respectively, which is more costly than a 24-week or 48-week course of Peg-IFN/RBV (\$9,300 to \$20,500).

Other Discussion Points:

CDEC noted the following:

- Resistance testing before therapy may identify the patients who will not respond to a given direct-acting antiviral drug, avoiding ineffective regimens and unnecessary costs. The identification and interpretation of resistance testing results continues to evolve.
- Patient enrolment in all trials was based on liver biopsy. The non-invasive diagnostic tests for fibrosis widely used in clinical practice are recognized to be reliable for F0 and F4 (cirrhosis), but less reliable for differentiating intermediate fibrosis grades.

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- The therapeutic approach to HCV is evolving rapidly as many highly effective, fully oral regimens of direct-acting antiviral drugs without Peg-IFN and/or RBV are emerging.

Research Gaps:

CDEC noted that there is limited evidence or an absence of evidence regarding the following:

- Comparative trials of SOF with other direct-acting antiviral drugs.
- Long-term outcomes with respect to the impact of SOF treatment on fibrosis or hepatocellular carcinoma, liver transplant, and mortality.
- Efficacy and safety data for patients who have undergone a liver transplant and patients with HIV coinfection.
- Re-infection rates, adherence to treatment, and toxicities in real-world settings, given that some HCV patients are injection drug users.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

July 15, 2014 Meeting

Regrets:

None

Conflicts of Interest:

None

About this Document:

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The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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