CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

SOFOSBUVIR
(Sovaldi — Gilead Sciences Canada Inc.)
Indication: Chronic Hepatitis C Infection

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated August 20, 2014.

Recommendation:
CDEC recommends that sofosbuvir (SOF) be reimbursed 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 2 CHC infection, in combination with ribavirin (RBV)
- Patients with genotype 3 CHC infection, in combination with RBV
- Patients with genotype 4 CHC infection in combination with pegylated-interferon and ribavirin (PR):
  - For patients who have not been previously treated with PR and do not have cirrhosis.

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 + PR achieved high rates of sustained virologic response (SVR) 12 for treatment-naive patients with genotype 1 CHC. However, given the adverse events associated with PR therapy and the availability of PR-free regimens for the treatment of genotype 1 CHC, SOF + PR is not recommended for patients with genotype 1 CHC.
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.

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3. At the submitted price, CDEC concluded that SOF + PR is likely to be cost-effective for patients with genotype 1 CHC who are treatment-naive and patients with genotype 2 CHC who are treatment experienced with PR or have a medical contraindication to PR. 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 PR or have a medical contraindication to PR.
4. CADTH's cost-effectiveness analysis in the *Therapeutic Review of Drugs for Chronic Hepatitis C Infection* demonstrated that treatment of CHC is likely cost-effective across all Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) scores based on generally accepted thresholds. Jurisdictions will need to consider the cost impact to drug plans and overall health care system sustainability in making decisions regarding treatment eligibility.

Of Note:

- CDEC noted that the severity of liver disease in patients with CHC infection is assessed primarily by fibrosis staging using METAVIR scores, and most clinicians consider a METAVIR score ≥ F2 to define more severe disease. Extrahepatic manifestations are additional considerations in defining disease severity.
- All patients with CHC infection should be considered for treatment, regardless of fibrosis score. Given the potential impact on health system sustainability of treating all patients with CHC infection on a first-come basis, priority for treatment should be given to patients with more severe disease.

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 (DAA) 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 co-infection.
- Re-infection rates, adherence to treatment, and toxicities in real-world settings, given that some patients with the hepatitis C virus (HCV) are injection drug users.

Other Discussion Points:

CDEC noted the following:

- Resistance testing before therapy may identify the patients who will not respond to a given DAA drug, avoiding ineffective regimens and unnecessary costs. The clinical use 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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Background:
SOF is a nucleotide polymerase inhibitor and the first DAA drug against the HCV 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 PR 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 + PR 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.

Submission History:
In August 2014, CDEC recommended that SOF be listed for the treatment of 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 PR:
  - 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 PR or a medical contraindication to PR.
- Patients with genotype 3 CHC infection, in combination with RBV:
  - a fibrosis stage of F2, F3, or F4
  - previous treatment experience with PR or a medical contraindication to PR.

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.

As part of a CADTH Therapeutic Review (*Drugs for Chronic Hepatitis C Infection*), CDEC issued evidence-informed recommendations in November 2015 to address the optimal use of all currently available interferon (IFN)-free treatments for CHC infection for multiple genotypes.

1. All patients with CHC infection should be considered for treatment, regardless of fibrosis score. Given the potential impact on health system sustainability of treating all patients with CHC infection on a first-come basis, priority for treatment should be given to patients with more severe disease.
2. Ledipasvir (LDV)/SOF and ombitasvir/paritaprevir/ritonavir (OMB/PAR/RIT) + dasabuvir DAS ± RBV as preferred regimens for treatment-naive and PR-experienced patients with CHC genotype 1 infection, regardless of cirrhosis status.
3. The following are preferred regimens for patients with CHC infection genotypes 2 through 4:

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- genotype 2: SOF/RBV for 12 weeks
- genotype 3 without cirrhosis: daclatasvir (DCV) + SOF for 12 weeks
- genotype 3 with cirrhosis: SOF/RBV for 24 weeks
- genotype 4 treatment-naive without cirrhosis: SOF + PR for 12 weeks.

4. CDEC considered there to be insufficient evidence to make a recommendation for patients with genotype 4 CHC who are treatment experienced or with cirrhosis regardless of treatment experience, genotype 5 CHC, and genotype 6 CHC.

The CADTH Common Drug Review (CDR)-participating jurisdictions submitted a request for advice to ask CDEC if the recommendation for SOF should be updated to align with the CDEC recommendations from the *Therapeutic Review of Drugs for Chronic Hepatitis C Infection*.

Summary of CDEC Considerations:
CDEC considered the following to address the request for advice:

- Materials included in the CDEC brief for the 2014 CDR review of SOF.
- The 2015 CDEC recommendation for SOF (August 20, 2014).
- The CDEC recommendations from the *Therapeutic Review of Drugs for Chronic Hepatitis C Infection*.
- The CDR request for advice brief, which included a detailed comparison of the key reasons and evidence underlying the CDEC recommendation for SOF and the CDEC recommendations from the *Therapeutic Review of Drugs for Chronic Hepatitis C Infection*.
- Input from five patient groups, which described the impacts of hepatitis C infection and expectations of therapy.

Comparison of CDEC Recommendations:

Patients with Genotype 1 CHC
For patients with genotype 1 CHC infection, CDEC's recommendation in the initial CDR review stated that SOF, in combination with PR, should be listed for treatment-naive patients with a liver fibrosis stage of ≥ 2. CDEC noted in the recommendation document that the therapeutic approach to treating CHC is evolving rapidly and that many highly effective, fully oral regimens of DAA drugs without PR or RBV were emerging. For the therapeutic review (TR), CDEC recommended two PR-free regimens (LDV/SOF and OMB/PAR/RIT + DAS) as the preferred options for patients with genotype 1. In addition, the TR included a recommendation that all patients with CHC infection should be considered for treatment, regardless of fibrosis score.

Patients with Genotype 2 CHC
For patients with genotype 2 CHC infection, CDEC's recommendation stated that SOF, in combination with RBV, be listed for patients with a liver fibrosis stage of ≥ 2 who are PR-experienced or have a medical contraindication to PR. In contrast to the initial CDEC recommendation for SOF, when considering the findings of CADTH's TR, CDEC recommended SOF as the preferred option for patients with genotype 2 CHC regardless of treatment experience, fibrosis stage, or cirrhosis status.

Key differences between the CDR and TR recommendations are as follows:

- The TR recommendations for SOF/RBV are less restrictive than the original CDEC recommendation with respect to the stage of liver fibrosis. Specifically, the TR

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recommendations do not impose restrictions based on liver fibrosis stage; whereas, the original CDEC recommendation was limited to patients with a liver fibrosis stage of ≥ 2.
- The TR recommendations for SOF/RBV are less restrictive with respect to patients who are PR-naive, as these recommendations no longer contain the clinical criterion that a patient demonstrate a medical contraindication to PR in order to be eligible for treatment with SOF.

Patients with Genotype 3 CHC

For patients with genotype 3 CHC infection, CDEC's recommendation stated that SOF, in combination RBV, be listed for patients with a liver fibrosis stage of ≥ 2 who are PR-experienced or have a medical contraindication to PR. The TR recommendations stated that SOF/RBV for 24 weeks is the preferred regimen for patients with genotype 3 CHC who have cirrhosis, regardless of whether or not a patient was previously treated with PR.

Key differences between the CDR and TR recommendations are as follows:
- The TR recommendations for SOF/RBV are somewhat more restrictive than the original CDEC recommendation with respect to the stage of liver fibrosis (i.e., ≥ 2 versus cirrhosis). This is due to the CADTH pharmacoeconomic evaluation demonstrating that DCV + SOF for 12 weeks is more cost-effective than SOF/RBV for 24 weeks for patients with genotype 3 CHC without cirrhosis.
- The TR recommendations for SOF/RBV are less restrictive with respect to patients who are PR-naive, as these recommendations no longer contain the clinical criteria that a patient demonstrate a medical contraindication to PR in order to be eligible for treatment with SOF.

Patients with Genotype 4 CHC

Although SOF was indicated for the treatment of genotype 4 CHC at the time of the initial CDR review, the manufacturer did not include this indication in their submission. In the absence of a pharmacoeconomic evaluation for patients with genotype 4 CHC, CDEC was unable to make a recommendation regarding this patient population. In contrast, CADTH included patients with genotype 4 CHC in the TR and CDEC recommended that SOF + PR for 12 weeks be the preferred treatment option for PR-naive patients without cirrhosis. CDEC concluded that there was insufficient evidence to make a recommendation for the following genotype 4 CHC patient populations:
- PR-naive patients with cirrhosis
- PR-experienced patients with or without cirrhosis.

Summary of Patient Input for the Current Request for Advice:

Five patient groups, the Canadian Liver Foundation, Action Hepatitis Canada, the Pacific Hepatitis C Network, the Canadian Treatment Action Council (CTAC), and the HepCBC Hepatitis C Education and Prevention Society, responded to the CDR call for patient input.
- Patient groups supported that all patients with CHC infection should be considered for treatment, regardless of fibrosis score. It was acknowledged that, should drug plans be unable to provide coverage for all patients, priority should be given to those with more severe disease.
- In general, patients are willing to tolerate treatment with RBV in order to increase their chances of successfully achieving SVR. Patients noted that the adverse effects associated with RBV are much less severe than those associated with pegylated-interferon (Peg-IFN).

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Evidence from the CDR Review of 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 PR in a treatment-naive 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-naive 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 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 the LLOQ during the post-treatment period, or having achieved HCV RNA less than the LLOQ at the end of treatment, confirmed with two consecutive values or the 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 problems, 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%.

Efficacy

<u>Genotypes 1 and 4</u>

- 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%)

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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 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 PR 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 PR 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 PR (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 group; 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 PR 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 the PR group ($P = 0.012$).
  - 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.

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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 PR.
  - 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 PR.
  - 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 PR.
  - 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.
  - VALENCE: <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 + PR for 12 weeks was compared with telaprevir (TEL) + PR, boceprevir (BOC) + PR, and PR alone. In genotype 2 patients, SOF/RBV for 12 weeks was compared with PR alone or no treatment. In genotype 3 patients, SOF/RBV for 16 weeks was compared with PR 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 TEL and BOC, and from IDEAL for PR (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 PR 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

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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 PR 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 DAA drugs and PR.
- 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 TEL, BOC, and PR 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 PR, TEL, and BOC 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 PR was $135,391 per QALY, and SOF was dominated by TEL and BOC. In patients with cirrhosis, using the lower bound of the 95% CI for SOF and assuming a 15% higher SVR rate for TEL and BOC, the ICUR for SOF was $7,119 per QALY versus PR and $3,237 per QALY versus BOC, but was dominated by TEL.
- In genotype 2 patients ineligible to receive PR, 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 PR, except in patients with cirrhosis where the ICUR was $62,162 versus PR. In genotype 2 prior non-responders, the ICUR for SOF compared with no treatment or PR were less attractive in patients without cirrhosis (ranging from $61,564 to $136,936), and SOF was dominated by PR and no treatment in patients with cirrhosis.

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- In genotype 3 patients ineligible to receive PR, 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 PR 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 PR, 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 (SIM) ($39,605, including wholesaler mark-up as SIM was not listed on any participating drug plans at the time of the SOF review) or TEL ($34,968), or a 24-week course of BOC ($25,200), but less costly than a 44-week course of BOC ($46,200).

When considering the cost of treatment regimens for genotype 1 patients (treatments used in combination with PR), SOF (with a 12-week course of PR, [redacted]) is more costly than SIM or TEL with a 24-week course of PR (approximately $49,110 and $44,470 respectively), as well as a 24-week course of BOC with a 28-week or 48-week course of PR (approximately $36,280 and $44,200 respectively), but less costly than SIM or TEL regimens with a 48-week course of PR (approximately $58,610 and $53,970 respectively), and a 44-week course of BOC with a 48-week course of PR (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 PR ($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 PR ($9,300 to $20,500).

Evidence from the CADTH Therapeutic Review:

Efficacy and Safety

Treatment-Naive Patients with Genotype 1 CHC

- For treatment-naive patients with genotype 1 CHC, all of the DAA treatment strategies under review, with the exception SIM/SOF for 12 weeks, significantly improved SVR compared with PR for 48 weeks (RR range 1.48 to 1.86). LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS ± RBV for 12 weeks significantly improved SVR compared with SOF/RBV for 24 weeks, response-guided therapy with SIM + PR, and SOF + PR for 12 weeks (result was statistically non-significant for OMB/PAR/RIT + DAS for 12 weeks versus SOF + PR for 12 weeks). There were no statistically significant differences between LDV/SOF for 12 weeks, DCV + SOF for 12 weeks, and OMB/PAR/RIT + DAS ± RBV for 12 weeks.
- Results of the subgroup analysis were consistent with those for the overall treatment-naive population, especially for the comparisons between IFN-free regimens; there were no significant differences in SVR 12 among LDV/SOF for 12 weeks, DCV + SOF for 12 weeks, and OMB/PAR/RIT + DAS ± RBV for 12 weeks where these regimens could be compared with one another.
- LDV/SOF for 12 weeks, OMB/PAR/RIT + DAS ± RBV for 12 weeks, and DCV + SOF for 12 weeks were associated with significantly lower risks for anemia than PR-based treatments, but only LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS for 12 weeks were significantly associated with less rash and depression compared with PR-based treatments. For rash, OMB/PAR/RIT + DAS + RBV for 12 weeks was less favourable than LDV/SOF for 12 weeks.

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There was no significant difference between DCV + SOF for 12 weeks and any of the IFN-free regimens.
- For anemia, OMB/PAR/RIT + DAS ± RBV for 12 weeks was less favourable than LDV/SOF for 12 weeks. There was no significant difference between DCV + SOF for 12 weeks and OMB/PAR/RIT + DAS ± RBV for 12 weeks or LDV/SOF for 12 weeks on this outcome.

Treatment-Experienced Patients with Genotype 1 CHC
- All of the DAA treatment strategies significantly improved SVR compared with PR (RR ranged from 2.72 to 3.75). There were no significant differences found when LDV/SOF for 12 weeks was compared with OMB/PAR/RIT + DAS ± RBV for 12 weeks. There were no trials for DCV + SOF in treatment-experienced patients.
- Results of the subgroup analyses were generally consistent with those for the overall treatment-experienced population in that no significant differences in SVR were found in most subgroups when LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS ± RBV for 12 weeks were compared against each other. One exception was the subgroup analysis of patients without cirrhosis, in which OMB/PAR/RIT + DAS + RBV for 12 weeks significantly improved SVR compared with LDV/SOF for 12 weeks. Due to the lack of stratified baseline data by prior treatment experience for OMB/PAR/RIT + DAS ± RBV for 12 weeks, this regimen was included only in the analysis of patients with cirrhosis as part of a sensitivity analysis based on certain assumptions.
- LDV/SOF for 12 weeks could not be included in any of the subgroup analyses by type of prior response — i.e., prior relapse, prior partial response, and prior null response — due to lack of data. As well, analysis by type of prior response was not possible for IFN-free regimens in patients with cirrhosis, due to lack of data.
- LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS for 12 weeks were associated with significantly less rash than PR-based treatments, and LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS ± RBV for 12 weeks were associated with significantly less anemia than PR-based treatments.
- For rash there was no significant difference between OMB/PAR/RIT + DAS ± RBV for 12 weeks and LDV/SOF for 12 weeks.
- For anemia, OMB/PAR/RIT + DAS + RBV for 12 weeks was less favourable than OMB/PAR/RIT + DAS for 12 weeks and LDV/SOF for 12 weeks.

Treatment-Naive Patients with Genotype 2 CHC
- Compared with PR for 24 weeks, SOF/RBV for 12 weeks significantly improved SVR; whereas, SOF + PR for 12 weeks was not significantly different from PR for 24 weeks (RRs ranged from 1.13 to 1.20). There was no significant difference between SOF/RBV for 12 weeks and SOF + PR for 12 weeks. There was no evidence for DCV + SOF for 24 weeks (the approved duration) in genotype 2 infection treatment-naive patients that could be incorporated into the NMA.
- For patients with cirrhosis, SOF/RBV for 12 weeks significantly improved SVR in genotype 2 treatment-naive patients compared with PR for 24 weeks.
- For patients without cirrhosis, only SOF/RBV for 12 weeks significantly improved SVR compared with PR for 24 weeks. There was no significant difference in SVR between SOF/RBV for 12 weeks and SOF + PR for 12 weeks.

Treatment-Experienced Patients with Genotype 2 CHC
- Neither SOF/RBV for 16 weeks nor SOF + PR for 12 weeks significantly improved SVR compared with SOF/RBV for 12 weeks (RRs ranged from 0.86 to 1.07), but SOF + PR for 12

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weeks significantly improved SVR when compared with SOF/RBV for 16 weeks. There was no evidence for DCV + SOF for 24 weeks (the approved duration) in treatment-experienced patients with genotype 2 infection that could be incorporated into the NMA.
- Results of subgroup analyses were generally consistent with those for the overall treatment-experienced population, although SOF/RBV for 16 weeks could not be included in the analysis of patients without cirrhosis.
- For patients with cirrhosis, there were no statistically significant differences in SVR between SOF/RBV for 12 weeks, SOF/RBV for 16 weeks, and SOF + PR for 12 weeks.
- For patients without cirrhosis, SOF + PR for 12 weeks did not significantly improve SVR when compared with SOF/RBV for 12 weeks.

Treatment-Naive Patients with Genotype 3 CHC
- Compared with PR for 48 weeks, SOF/RBV for 24 weeks, DCV + SOF for 12 weeks, and SOF + PR for 12 weeks significantly improved SVR (RRs ranged from 1.31 to 1.37), and there were no significant differences between these regimens.
- Results of subgroup analyses were consistent with those for the overall treatment-naive population, although DCV + SOF for 12 weeks could not be included in the subgroup analysis of patients with cirrhosis due to lack of data.
- For patients with cirrhosis, SOF/RBV for 24 weeks significantly improved SVR compared with PR for 48 weeks. There was no significant difference between SOF 12 + PR 12 and SOF/RBV for 24 weeks.
- For patients without cirrhosis, SOF/RBV for 24 weeks, DCV + SOF for 12 weeks, and SOF + PR for 12 weeks significantly improved SVR compared with PR for 48 weeks. There were no significant differences between these three regimens.
- LDV/SOF for 12 weeks, OMB/PAR/RIT + DAS ± RBV for 12 weeks, and DCV + SOF for 12 weeks were associated with significantly lower risks for anemia than PR-based treatments, but only LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS for 12 weeks were significantly associated with less rash and depression compared with PR-based treatments. For rash, OMB/PAR/RIT + DAS + RBV for 12 weeks was less favourable than LDV/SOF for 12 weeks. There was no significant difference between DCV + SOF for 12 weeks and any of the IFN-free regimens.
- For anemia, OMB/PAR/RIT + DAS ± RBV for 12 weeks was less favourable than LDV/SOF for 12 weeks. There was no significant difference between DCV + SOF for 12 weeks and OMB/PAR/RIT + DAS ± RBV for 12 weeks or LDV/SOF for 12 weeks on this outcome.

Treatment-Experienced Patients with Genotype 3 CHC
- Compared with PR for 48 weeks, SOF/RBV for 24 weeks, DCV + SOF for 12 weeks, and SOF + PR for 12 weeks significantly improved SVR (RRs ranged from 1.52 to 1.72). No statistically significant differences were observed between these three regimens.
- Results of subgroup analyses were consistent with those for the overall treatment-experienced population; however, there were no statistically significant differences in SVR rates in the subgroup of patients without cirrhosis between SOF + PR for 12 weeks and PR for 48 weeks. There was no evidence for DCV + SOF 24 weeks (the approved duration) that could be analyzed in the NMA of patients with genotype 3 infection and cirrhosis.
- For patients with cirrhosis, SOF/RBV for 24 weeks and SOF + PR for 12 weeks significantly improved SVR compared with PR for 48 weeks. There was no significant difference between SOF/RBV for 24 weeks and SOF + PR for 12 weeks.

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- For patients without cirrhosis, SOF/RBV for 24 weeks, DCV + SOF for 12 weeks and SOF 12 + PR 12 significantly improved SVR compared with PR for 48 weeks There was no significant differences between SOF 24 + RBV 24, DCV + SOF for 12 weeks, and SOF + PR for 12 weeks.
- LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS for 12 weeks were associated with significantly less rash than PR-based treatments, and LDV/SOF for 12 weeks and OMB/PAR/RIT + DAS ± RBV for 12 weeks were associated with significantly less anemia than PR-based treatments.
- For rash there was no significant difference between OMB/PAR/RIT + DAS ± RBV for 12 weeks and LDV/SOF for 12 weeks.
- For anemia, OMB/PAR/RIT + DAS + RBV for 12 weeks was less favourable than OMB/PAR/RIT + DAS for 12 weeks and LDV/SOF for 12 weeks.

Cost-Effectiveness

CADTH conducted a CUA of drugs for CHC infection using an updated version of the model used for the 2014 CADTH TR of treatments for CHC infection. The primary outcome was the number of QALYs, with treatments compared in terms of the incremental cost per QALY. Treatment effect estimates for SVR and adverse events (anemia, depression, and rash) were obtained from the CADTH systematic review and NMA. Other inputs for the economic model were derived from published sources and validated by clinical experts. Drug costs were obtained from the Ontario Drug Benefit Exceptional Access Program, Yukon Drug Formulary, the Saskatchewan Drug Plan, or directly from manufacturers.

Patients with Genotype 1 CHC

The base-case analysis suggested that for each genotype 1 population (i.e., treatment-naive non-cirrhotic, treatment-naive cirrhotic, treatment-experienced non-cirrhotic, or treatment-experienced cirrhotic), at least one of the IFN-free therapies appeared to be economically attractive compared with PR alone (ICURs less than $30,000 per QALY). The drug that is most cost-effective varied by population, but was generally consistent across fibrosis stages.

For patients with genotype 1 CHC infection who are treatment-naive and non-cirrhotic, at a willingness to pay (λ) of $50,000 per QALY, OMB/PAR/RIT + DAS for 12 weeks was likely to be the most cost-effective option compared with PR alone. For patients with genotype 1 CHC infection who are treatment-naive and cirrhotic, LDV/SOF for 12 weeks was likely to be the most cost-effective option compared with PR alone. The analysis also suggests that for patients with genotype 1 CHC infection who are treatment-experienced and non-cirrhotic, OMB/PAR/RIT + DAS for 12 weeks was likely to be the most cost-effective option compared with PR alone at a willingness to pay of $50,000 per QALY. For patients with genotype 1 CHC infection who are treatment-experienced and cirrhotic, response-guided therapy with SIM/PR was likely to be the most cost-effective option, followed by LDV/SOF + RBV for 12 weeks compared with PR alone. The incremental QALYs for OMB/PAR/RIT + DAS for 12 weeks and LDV/SOF for 12 weeks compared with PR were similar in all analyses.

Patients with Genotype 2 CHC

For patients with genotype 2 CHC infection, who are treatment-naive and non-cirrhotic, the IFN-free or the PR-based DAA therapies do not appear to be economically attractive compared with PR alone (ICURs exceeded $200,000 per QALY). For patients who are treatment-naive with cirrhosis and those who are treatment-experienced without cirrhosis, SOF/RBV for 12 weeks was the most cost-effective option, with an ICUR of less than $60,000 per QALY (versus PR for

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treatment-naive patients, and versus no treatment for treatment-experienced patients). For patients who are treatment-experienced with cirrhosis, SOF + PR for 12 weeks was the most cost-effective option when compared with no treatment (ICUR of $18,226 per QALY), but it is currently not approved for this population; SOF/RBV for 12 weeks was the most cost-effective option that is approved in Canada (ICUR $21,338 per QALY).

Patients with Genotype 3 CHC

In the base-case analysis for genotype 3 infection, the IFN-free or the PR-based DAA therapies do not appear to be economically attractive compared with PR alone for treatment-naive patients without cirrhosis (ICURs exceeded $150,000 per QALY). In patients who are treatment-naive with cirrhosis, SOF/RBV for 24 weeks was the most cost-effective approved option with an ICUR of $92,117 when compared with PR for 48 weeks. For patients who are treatment-experienced with or without cirrhosis, SOF/RBV for 24 weeks was the most cost-effective approved option (ICUR approximately $40,000 per QALY compared with no treatment). In exploratory analyses where DCV + SOF for 12 weeks was included in analyses of patients without cirrhosis regardless of treatment experience, this regimen was the most cost-effective among the approved regimens (ICURs $28,151 and $97,158 per QALY for treatment-experienced and treatment-naive patients respectively). However, the unapproved regimen SOF + PR for 12 weeks was the most cost-effective regimen versus PR in treatment-naive patients with genotype 3 infection (ICUR $70,792 per QALY), and versus no treatment for treatment-experienced patients, regardless of cirrhosis status (ICURs for patients with and without cirrhosis < $21,000 per QALY). In relation to SOF + PR for 12 weeks, the most cost-effective approved treatments for genotype 3 infection were either associated with very high ICURs, or were dominated.

Patients with Genotype 4 CHC

In the base-case analysis for patients with genotype 4 infection who are treatment-naive, no DAA-based regimen was found to be cost-effective in patients without cirrhosis (ICURs exceeded $200,000 per QALY). For patients who are treatment-naive with cirrhosis or those who are treatment-experienced, SOF/RBV for 24 weeks was considered the most cost-effective treatment (ICUR less than $60,000 per QALY), but is not currently indicated. SOF + PR for 12 weeks, the only approved treatment for genotype 4 infection, was included in an exploratory analysis of treatment-naive, non-cirrhotic patients with genotype 4 infection; this regimen was associated with an ICUR of $63,421 per QALY compared with PR

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April 20, 2016 Meeting
Regrets:

One CDEC member was unable to participate in this portion of the meeting.

Conflicts of Interest:

None

About This Document:

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