



CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

SOFOSBUVIR/VELPATASVIR

(Eplclusa — Gilead Sciences Canada, Inc.)

Indication: Chronic Hepatitis C Virus Infection in Adults

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that sofosbuvir/velpatasvir (SOF/VEL) be reimbursed for the treatment of chronic hepatitis C (CHC) infection, if the following criterion and condition are met:

Criterion:

- Treatment should be initiated by physicians with experience in the management of patients with CHC.

Condition:

- Reduced price.

Reasons for the Recommendation:

1. High rates of sustained virologic response at 12 weeks (SVR12) were observed across all genotypes and among treatment-naive and previously treated patients in the four trials reviewed. In the ASTRAL-1 study, the SVR12 rate was 99.0% (95% confidence interval [CI], 97.9% to 99.6%) in treatment-naive and previously treated patients with chronic genotype 1, 2, 4, 5, or 6 hepatitis C virus (HCV) infection who received SOF/VEL for 12 weeks. In the ASTRAL-2 study, the SVR12 rate was 99.3% (95% CI, 95.9% to 100%) in treatment-naive and previously treated patients with chronic genotype 2 HCV infection who received SOF/VEL for 12 weeks, which was statistically noninferior and statistically superior to sofosbuvir plus ribavirin (SOF + RBV) for 12 weeks. In the ASTRAL-3 study, the SVR12 rate was 95.3% (95% CI, 92.1% to 97.5%) in treatment-naive and previously treated patients with chronic genotype 3 HCV infection who received SOF/VEL for 12 weeks, which was statistically superior to SOF + RBV for 24 weeks. In the ASTRAL-4 study, the SVR12 rate was 94.3% (95% CI, 87.1% to 98.1%) in treatment-naive and previously treated patients with chronic genotypes 1, 2, 3, or 4 HCV infection with decompensated cirrhosis who received SOF/VEL + RBV for 12 weeks.
2. There is insufficient evidence that the new treatment is superior to the least costly alternative.
3. The true incremental cost-effectiveness of SOF/VEL versus other interferon (IFN)-free regimens is uncertain in the various patient populations considered. For genotype 1 infections, the most common type in Canada, SOF/VEL is dominated in the setting of treatment-naive, non-cirrhotic patients by other non-pegylated interferon plus ribavirin (PR) treatments.

Of Note:

Jurisdictions may consider the cost impact to drug plans and overall health care system sustainability in making decisions regarding treatment eligibility. The drug plan cost of treatment with the drug under review should not exceed the drug plan cost of treatment with the least costly alternative interferon-free option.

Research Gaps:

The Committee proposed that the following issues be addressed through research as a high priority:

1. Patients with active substance abuse or who were coinfecting with HIV or hepatitis B virus were excluded from the studies reviewed by the CADTH Common Drug Review (CDR). These patient groups represent important subgroups to which future research should be directed to understand the generalizability of study results to these populations.
2. The science regarding resistance-associated variants (RAVs) is evolving rapidly. Increased understanding of how and when such variants are important may be relevant in the near future for revising reimbursement criteria.

Background:

Epclusa is a fixed-dose combination of SOF and VEL. Both SOF and VEL exhibit high potency and specificity as individual agents against HCV as compounds that target the HCV nonstructural protein 5B (NS5B) and 5A (NS5A), respectively. SOF is a pan-genotypic polymerase inhibitor of the HCV NS5B ribonucleic acid (RNA)-dependent RNA polymerase. VEL is a pan-genotypic HCV inhibitor targeting the HCV NS5A protein. Epclusa has a Health Canada indication for use alone for the treatment of chronic HCV infection in adults without cirrhosis or with compensated cirrhosis; in addition, Epclusa has a Health Canada indication for use in combination with RBV for the treatment of CHC infection in adults with decompensated cirrhosis. Epclusa is formulated in a single tablet; the tablet is composed of 400 mg SOF and 100 mg VEL. The recommended dosage is one tablet daily of Epclusa for 12 weeks for patients without cirrhosis and patients with compensated cirrhosis, and one tablet daily of Epclusa plus weight-based RBV for 12 weeks for patients with decompensated cirrhosis.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: A systematic review of randomized controlled trials and pivotal studies of SOF/VEL, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to individuals with CHC infection.

Patient Input Information:

Patient input was contributed by the Canadian Liver Foundation, the Gastrointestinal (GI) Society, Canadian Treatment Action Council, the Pacific Hepatitis C Network, and the Hepatitis C Education and Prevention Society (HepCBC). Information was gathered through interviews with patients and caregivers affected by CHC, nurse specialists, gastroenterologists, hepatologists, and pharmacists, surveys, meetings with support groups, and a webinar that included patients diagnosed with CHC. CDEC heard the following:

- Patients experience a variety of physical symptoms, as well as anxiety, depression, stigma, and isolation as a result of CHC. They and their families also often bear serious financial hardships.

- Patients describe the weight of their worry when they cannot get access to treatments because they are not yet sick enough or because they simply cannot afford the very high costs.
- Patients expect high cure rates with SOF/VEL. They also expect it to work particularly well in patients who were null responders to other direct-acting antivirals (DAAs), in patients who relapsed after taking a DAA, in those with either compensated or decompensated cirrhosis, and in those infected with rare and/or multiple HCV genotypes.
- Patients see that one pill a day with SOF/VEL has advantages over most other treatments.
- Many patients stress the value of having access to as many effective treatments as possible, while some express the hope that SOF/VEL can be a “one-pill-fits-all” therapy.

Clinical Trials

The CDR systematic review included four phase 3 clinical trials (ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4). All trials were randomized and multi-centre. ASTRAL-1 was double blind, while ASTRAL-2, ASTRAL-3, and ASTRAL-4 were open label. ASTRAL-1 (N = 741) assessed the efficacy and safety of SOF/VEL for 12 weeks compared with placebo among treatment-naïve and previously treated patients with chronic genotype 1, 2, 4, 5, or 6 HCV infection, including those with compensated cirrhosis. ASTRAL-2 (N = 269) assessed the efficacy and safety of 12 weeks of the SOF/VEL treatment compared with 12 weeks of SOF + RBV treatment in treatment-naïve and previously treated patients with chronic genotype 2 HCV infection, including those with compensated cirrhosis. ASTRAL-3 (N = 558) assessed the efficacy and safety of 12 weeks of the SOF/VEL treatment compared with 24 weeks of SOF + RBV treatment in treatment-naïve and previously treated patients with chronic genotype 3 HCV infection, including those with compensated cirrhosis. ASTRAL-4 (N = 268) assessed the efficacy and safety of SOF/VEL + RBV for 12 weeks in treatment-naïve and previously treated patients with chronic genotypes 1 through 6 who had decompensated cirrhosis (classified as Child–Turcotte–Pugh [CTP] class B).

Outcomes

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

- SVR12 — defined as HCV RNA less than the lower limit of quantification (LLOQ) 12 weeks after discontinuation of all study drugs.
- Relapse — defined as having HCV RNA greater than or equal to LLOQ during the post-treatment period after having achieved HCV RNA less than LLOQ at end of treatment (EOT), confirmed with two consecutive values or last available post-treatment measurement.
- Short Form (36) Health Survey (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 (HRQoL). SF-36 consists of eight domains: Physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. SF-36 also provides two component summaries: The physical component summary and the mental component summary.
- Chronic Liver Disease Questionnaire (CLDQ) — an instrument used to assess the HRQoL for patients with chronic liver disease. CLDQ measures activity/energy, emotion, worry, and systemic symptoms, which are combined in the CLDQ total score. All domains and the total score are based on a Likert scale of 0 (worst) to 7 (best).
- Functional Assessment of Chronic Illness Therapy–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).

- EuroQol Visual Analogue Scale (EQ VAS) — a 20 cm visual analogue scale that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state”.
- Work Productivity and Activity Impairment (WPAI) questionnaire — an instrument used to measure the impact of a disease on work and on daily activities.
- CTP and Model for End-Stage Liver Disease (MELD) — used to stage disease severity in patients with end-stage liver disease. The CTP and MELD are prognostic tools to classify patients with cirrhosis according to severity of disease. Both the CTP and MELD have been used to rank liver transplant candidates, with the MELD replacing the CTP in 2002 as a more objective measure that was able to assess the risk of mortality.

The primary outcome of all studies was the proportion of patients with SVR12.

Efficacy

- In the ASTRAL-1 study, the SVR12 rate was 99.0% (95% CI, 97.9% to 99.6%) in treatment-naive and previously treated patients with chronic genotype 1, 2, 4, 5, or 6 HCV infection who received SOF/VEL for 12 weeks. The lower bound of the 95% CI (99.6%) exceeded the re-specified performance goal of 85%.
- In the ASTRAL-2 study, the SVR12 rate was 99.3% (95% CI, 95.9% to 100%) in treatment-naive and previously treated patients with chronic genotype 2 HCV infection who received SOF/VEL for 12 weeks, while the SVR12 rate in the SOF + RBV for 12 weeks treatment group was 93.9% (95% CI, 88.4% to 97.3%). The 12-week regimen of SOF/VEL was statistically noninferior to SOF + RBV for 12 weeks (SVR difference: 5.2%; 95% CI, 0.2% to 10.3%). Treatment with SOF/VEL for 12 weeks was shown to be statistically superior to SOF + RBV for 12 weeks, as demonstrated by the *P* value of 0.018.
- In the ASTRAL-3 study, the SVR12 rate was 95.3% (95% CI, 92.1% to 97.5%) in treatment-naive and previously treated patients with chronic genotype 3 HCV infection who received SOF/VEL for 12 weeks, while the SVR12 rate in the SOF + RBV for 24 weeks treatment group was 80.4% (95% CI, 75.2% to 84.9%). The strata-adjusted difference (95% CI) in the proportions was 14.8% (95% CI, 9.6% to 20.0%), demonstrating superiority of treatment with SOF/VEL for 12 weeks over SOF + RBV for 24 weeks for SVR12.
- In the ASTRAL-4 study, the SVR12 rate was 94.3% (95% CI, 87.1% to 98.1%) in treatment-naive and previously treated patients with chronic genotypes 1, 2, 3, or 4 HCV infection with decompensated cirrhosis who received SOF/VEL + RBV for 12 weeks. The SOF/VEL + RBV for 12 weeks treatment group met the primary efficacy end points with SVR12 rates that were statistically superior compared with the assumed spontaneous rate of 1%.
- In the ASTRAL-1 study, the high SVR12 rate was seen in all subgroups of patients (patients with cirrhosis, without cirrhosis, with prior treatment failure, treatment-naive, and previously treated with a DAA + PR). The SVR12 rate was high among genotype 1, 2, 4, 5, and 6 HCV-infected patients. There were two virologic failures among 624 patients treated with SOF/VEL; both had genotype 1 HCV infection and both relapsed by post-treatment week 4. Baseline NS5A or NS5B RAVs had no impact on SVR12, with high SVR12 across all HCV genotypes and subtypes regardless of the presence of RAVs.
- In the ASTRAL-2 study, treatment with SOF/VEL for 12 weeks resulted in high SVR12 rates with no virologic failures in patients with genotype 2 HCV infection, irrespective of treatment status, cirrhosis, and presence of baseline NS5A RAVs.
- In the ASTRAL-3 study, despite a high combined SVR12 rate in the SOF/VEL for 12 weeks treatment group of 95%, both prior treatment-experienced (64 of 71 patients: 90.1% SVR) and cirrhosis (73 of 80 patients: 91.3% SVR) patients had a moderate negative impact on treatment responses. In the patient group with both cirrhosis and prior treatment experience,

the SVR12 rate was 89% (33 of 37). The SVR12 rates were 89.1% (57 of 64) in patients who had received a prior PR regimen, and 85.0% (17 of 20) in patients who were non-responders to prior HCV treatment. In the SOF + RBV for 24 weeks treatment group, patients with cirrhosis had considerably lower SVR12 rates (55 of 83: 66.3%) than patients without cirrhosis (163 of 187: 87.2%), and patients with prior treatment experience had considerably lower SVR12 rates (45 of 71: 63.4%) than treatment-naive patients (176 of 204: 86.3%).

- In the ASTRAL-3 study, pre-treatment NS5A RAVs were present in 16% of patients, in the SOF/VEL for 12 weeks treatment group. There was a lower SVR12 rate in SOF/VEL-treated patients with baseline NS5A RAVs compared with patients without NS5A RAVs (88% versus 97%, respectively). In the SOF/VEL for 12 weeks treatment group, the Y93H was detected in 25 (9%) of patients with an SVR12 rate of 84% (21 of 25). A total of 10 patients in the SOF/VEL for 12 weeks treatment group relapsed, and one patient was reinfectd. All 10 patients had the NS5A RAV Y93H detected at relapse time points.
- In the ASTRAL-4 study that included patients with decompensated cirrhosis, treatment with SOF/VEL + RBV for 12 weeks resulted in high SVR12 rates irrespective of genotype, prior treatment history, or baseline HCV RNA. The presence of pre-treatment NS5A RAVs did not affect treatment outcome.
- The ASTRAL-4 study assessed improvement in MELD and CTP scores. In a significant proportion of patients who achieved SVR12 and who received SOF/VEL + RBV for 12 weeks, viral eradication was accompanied by a corresponding improvement in CTP and MELD scores in a high proportion of patients, (41 of 81 patients [50.6%] had improvement in MELD score; 33 patients [40.7%] had an improvement in CTP score). Twelve patients (14.8%) had no change in their MELD score, and 40 patients (49.4%) had no change in their CTP score.
- HRQoL was measured using the SF-36, and CLDQ-HCV in all four trials. Other patient-reported outcomes (PROs) in these trials included the FACIT-F Scale and the WPAI. In ASTRAL-1, among patients in the SOF/VEL for 12 weeks treatment group, there were statistically significant ($P < 0.05$) improvements in PROs compared with patients in the placebo group. Between baseline and post-treatment week 12, improvements were observed in SF-36 (domains of role physical, bodily pain, general health, vitality, social function, mental health, the physical component, and the mental component scores), CLDQ-HCV (overall score), FACIT-F (total score), and WPAI (per cent activity impairment). In the ASTRAL-2 and ASTRAL-3 studies, overall, results from the SF-36, CLDQ-HCV, FACIT-F, and WPAI Hep C quality-of-life questionnaires indicated that no decrements in quality of life among patients in the SOF/VEL for 12 weeks treatment group occurred at EOT. In ASTRAL-4, in the SOF/VEL + RBV for 12 weeks treatment group, at the EOT, decreases (worsening) from baseline were generally observed in four of eight domain scores of the SF-36 (domains of vitality, social functioning, role emotional, and mental health) and the mental component score.

Harms (Safety and Tolerability)

- The proportions of patients who experienced at least one adverse event were:
 - 68.7% to 88.4% while on SOF/VEL for 12 weeks
 - 90.8% among those who received SOF/VEL + RBV for 12 weeks
 - 76.5% among those who received SOF + RBV for 12 weeks
 - 94.5% among those who received SOF + RBV for 24 weeks
 - 76.7% among those who received placebo.
- The proportions of patients who experienced at least one serious adverse event were reported as follows:

- 1.5% to 2.4% while on SOF/VEL for 12 weeks
- 16.1% among those who received SOF/VEL + RBV for 12 weeks
- 1.5% among those who received SOF + RBV for 12 weeks
- 5.5% among those who received SOF + RBV for 24 weeks
- 0% among those who received placebo.
- The proportions of patients who experienced an adverse event leading to the discontinuation of any study drug was reported as follows:
 - 0.2% to 0.7% while on SOF/VEL for 12 weeks
 - 4.6% among those who received SOF/VEL + RBV for 12 weeks
 - 0%, among those who received SOF + RBV for 12 weeks
 - 3.3% among those who received SOF + RBV for 24 weeks
 - 1.7% among those who received placebo.

Cost and Cost-Effectiveness

The manufacturer submitted a price of \$714.29 per tablet of SOF/VEL or \$60,000 for a 12-week course. The addition of RBV to SOF/VEL is recommended for patients with CHC infection and decompensated cirrhosis, which increases the cost of the 12-week regimen to between \$63,045 and \$63,654, depending upon RBV dose.

The manufacturer submitted a cost-utility analysis comparing SOF/VEL against a number of comparators for each genotype, as well as SOF/daclatasvir (DCV) for non-cirrhotic patients with genotype 3 infection, and grazoprevir (GZR)/elbasvir (EBR). Some existing treatments (such as regimens containing pegylated interferon) were excluded for certain genotypes. The authors used a Markov cohort model consisting of 17 mutually exclusive health states representing Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) fibrosis scores (F0 to F4), decompensated cirrhosis, the distal consequences of CHC infection such as hepatocellular carcinoma and liver transplantation, and death. The patient cohort was assumed to have a mean age of 50 years at the start of the model and was followed up to 80 years of age. The perspective of the model was that of the Canadian publicly funded health care system. Many elements of the model closely followed the recent CADTH Therapeutic Review of treatments for CHC infection, including the natural history, utility figures, and some cost figures. Effectiveness parameters used in the model were drawn from trials (most of which were non-comparative) for the regimens of interest.

The manufacturer presented cost-effectiveness results for 26 separate subgroups defined by genotype, cirrhosis status, and prior treatment experience. In the analyses of patients without cirrhosis, SOF/VEL appeared to be cost-effective at a threshold of \$50,000 per quality-adjusted life-year (QALY) for treatment-naïve patients with genotype 2 infection and for treatment-experienced patients with genotypes 1a, 1b, 2, or 3 infection. For patients with compensated cirrhosis, SOF/VEL appeared to be cost-effective for patients with genotypes 1a, 2, and 3 infection. SOF/VEL + RBV was also cost-effective for patients with decompensated cirrhosis.

CDR identified a number of significant technical issues with the submitted analysis:

- The manufacturer's main results were reported as pairwise analyses of SOF/VEL ± RBV versus individual comparators. The appropriate approach would have been to conduct a combined analysis of all comparators and report sequential incremental cost-utility ratios (ICURs).
- Uncertainty in model parameters was handled inappropriately in probabilistic sensitivity analyses.

- Effectiveness parameters were drawn from non-comparative trials without a formal indirect comparison. The sample size for many subgroups was low, and the high degree of uncertainty in estimates from these subgroups was not accounted for appropriately in the model.
- For a number of subgroups, the model submitted to CDR did not include all relevant comparators.
- Costs of monitoring and for hepatocellular carcinoma appeared unrealistically high.

Many of these limitations were due to problems with the submitted model that could not be addressed through CDR reanalysis. Those limitations that could be addressed through reanalysis, such as cost inputs, were generally of lesser importance.

The reanalyses indicated that for treatment-naïve, non-cirrhotic patients, SOF/VEL was dominated (i.e., it was more costly and less effective) by ombitasvir/paritaprevir boosted with ritonavir + dasabuvir (OMB/PAR/r + DAS) for genotype 1a and 1b infection, while the ICUR was above \$50,000 per QALY versus PR for genotypes 2 and 3 infection. For treatment-naïve patients with compensated cirrhosis, SOF/VEL appeared to be cost-effective in genotypes 1a, 2, and 3 infection, while the ICUR exceeded \$140,000 per QALY against OMB/PAR/r + DAS + RBV in genotype 1b infection. For treatment-experienced patients, SOF/VEL appeared to be cost-effective irrespective of cirrhosis status for genotypes 1a, 2, and 3 infection, and for patients with genotype 1b infection without cirrhosis. It was dominated by OMB/PAR/r + DAS + RBV in patients with genotype 1b infection and cirrhosis. For patients with decompensated cirrhosis, SOF/VEL + RBV appeared to be cost-effective in both treatment-naïve and treatment-experienced patients. Interpretable reanalyses were not possible for genotypes 4 and 5/6 infection because of the lack of appropriate comparators in the model.

Due to the significant, unresolved limitations of the submitted economic analysis, the results (including CDR reanalyses) were deemed unreliable for decision-making. Accordingly, CDR considered there to be no basis on which to justify a price premium for SOF/VEL over other interferon-free regimens available for the treatment of CHC infection.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeyesundera.

September 21, 2016 Meeting:

Regrets:

Four CDEC members did not attend.

Conflicts of Interest:

None.

About This Document:

CDEC provides formulary reimbursement recommendations or advice to CDR-participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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