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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR (VOSEVI — GILEAD SCIENCES CANADA, INC.)
Indication: Chronic hepatitis C virus infection

RECOMMENDATION:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX; Vosevi) be reimbursed for the treatment of adult patients with chronic hepatitis C virus (HCV) infection, without cirrhosis or with compensated cirrhosis, who have: genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor; or genotype 1, 2, 3, or 4 infection and have been previously treated with an HCV regimen containing SOF without an NS5A inhibitor, if the following conditions are met:

Conditions:
- The patient is under the care of a physician with experience in the diagnosis and management of HCV infection.
- Drug plan cost for SOF/VEL/VOX should not exceed the drug plan cost for SOF/VEL.

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Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Recommendation:

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Conditions:

- The patient is under the care of a physician with experience in the diagnosis and management of HCV infection.
- The drug plan cost for SOF/VEL/VOX does not exceed the drug plan cost for SOF/VEL.

Reasons for the Recommendation:

1. Evidence from two randomized controlled trials demonstrated that high percentages of patients treated with SOF/VEL/VOX who had previously received direct-acting antiviral agents (i.e., DAA-experienced patients) achieved sustained virologic response at 12 weeks (SVR 12). In POLARIS-1 (N = 415), 96.2% (95% confidence interval [CI], 93.1% to 98.2%) of SOF/VEL/VOX-treated patients without cirrhosis or with compensated cirrhosis, and with genotype 1, 2, 3, 4, 5, or 6 chronic HCV infection who had previously been treated with a DAA regimen containing an NS5A inhibitor, achieved SVR 12. In POLARIS-4 (N = 333), 97.8% (95% CI, 94.5% to 99.4%) of patients without cirrhosis or with compensated cirrhosis, and with genotype 1, 2, 3, or 4 chronic HCV infection who had previously been treated with an HCV regimen without an NS5A inhibitor, achieved SVR 12 with SOF/VEL/VOX treatment for 12 weeks.
2. POLARIS-1 included a placebo treatment arm and POLARIS-4 included a SOF/VEL treatment arm. However, there were no statistical comparisons between treatment arms for the primary outcome of SVR 12. Therefore, the direct comparative benefits and harms of SOF/VEL/VOX versus SOF/VEL and other DAA-based regimens with respect to achieving sustained virologic response (SVR) in DAA-experienced patients are unknown.
3. Results from the manufacturer-provided cost-utility analysis suggested that SOF/VEL/VOX is a cost-effective treatment option in patients with all genotypes of chronic HCV infection who are NS5A-experienced, as well as in patients with genotypes 1 to 4 who are NS5A naïve, as compared with no treatment or treatment with SOF/VEL. The results of the CADTH Common Drug Review (CDR) reanalysis were similar to the manufacturer's base case results for non-cirrhotic patients. In the cirrhotic group, treatment with SOF/VEL/VOX was no longer dominant compared with no treatment or treatment with SOF/VEL but was still cost-effective. CDR identified several key limitations with the manufacturer-submitted cost-utility analysis that could not be addressed during reanalysis. Therefore, the true incremental cost-effectiveness of treatment with SOF/VEL/VOX versus no treatment or treatment with SOF/VEL is uncertain.

Discussion Points:

- CDEC noted that the efficacy of SOF/VEL/VOX for the primary outcome in both studies, SVR 12, was determined based on statistical comparison with a performance goal of 85% as opposed to direct statistical comparison with the other treatment arm in each study (placebo in POLARIS-1 and SOF/VEL in POLARIS-4). The method for establishing the performance goal of 85% was not clearly defined in either of the POLARIS trials.
- There were no comparisons between SOF/VEL/VOX and other Health Canada–approved DAA-based regimens for patients who are DAA treatment experienced, such as glecaprevir/pibrentasvir (Maviret). CDEC acknowledged that, because both products were developed at the same time, it was likely impractical for a head-to-head trial to be conducted.

- CDEC noted that SOF/VEL/VOX does not have a specific indication for patients with HCV infection who have been previously treated with pegylated interferon/ribavirin plus boceprevir, or telaprevir, or simeprevir, whereas glecaprevir/pibrentasvir does have this indication, although it is limited to patients with HCV genotype 1.
- The POLARIS trials enrolled small numbers of patients with genotypes that are less common. Only POLARIS-1 included patients with genotypes 5 and 6, and the sample sizes were very small: there was one patient with genotype 5 (who received SOF/VEL/VOX) and eight patients with genotype 6 (six received SOF/VEL/VOX and 2 received placebo). CDEC noted that the relative rarity of these specific HCV genotypes might have contributed to the small sample sizes.
- CDEC noted that the percentage of patients who achieved SVR 12 was consistent in both studies regardless of cirrhotic state and across a range of prior treatment experiences, including the number of previous DAA regimens. However, there were few patients in many of the cirrhosis and treatment experience subgroups, which contributed to the uncertainty in the clinical and cost analyses of SOF/VEL/VOX.
- Patients from HCV subpopulations of interest, such as those with severe renal impairment or HIV and/or hepatitis B virus coinfection, were excluded from the POLARIS trials. Therefore, the trials did not provide any data with respect to the effectiveness and safety of SOF/VEL/VOX in these subgroups of patients with HCV infection. The Committee noted that the product monograph for SOF/VEL/VOX contains a warning regarding the potential risk for hepatitis B virus re-activation, as do the product monographs for many other DAAs approved by Health Canada.
- CDEC noted that patients included in the POLARIS trials were treatment experienced with a DAA-containing regimen of at least four weeks in duration. The patients' most recent treatment had to have been completed at least eight weeks prior to trial screening and could not have been discontinued because of an adverse event or virologic failure due to nonadherence.

Background:

SOF/VEL/VOX has a Health Canada indication for the treatment of HCV infection in adult patients, without cirrhosis or with compensated cirrhosis, who meet one of the following conditions:

- The patient has experienced a genotype 1, 2, 3, 4, 5, or 6 infection and has previously been treated with an HCV regimen containing an NS5A inhibitor.
- The patient has experienced a genotype 1, 2, 3, or 4 infection and has been previously treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

These pan-genotypic DAAs belong to the NS3/4A protease inhibitor drug class (VOX) and the NS5A inhibitor drug class (VEL). SOF is a nucleotide analogue pan-genotypic NS5B polymerase inhibitor. SOF/VEL/VOX is available as a single table containing 400 mg of SOF, 100 mg of VEL, and 100 mg of VOX, and the Health Canada–approved dose is one tablet once daily with food for 12 weeks.

Summary of CDEC Considerations:

The Committee considered the following information prepared by CDR: a systematic review of randomized controlled trials of SOF/VEL/VOX and a critique of the manufacturer's pharmacoeconomic evaluation. The Committee also considered patient group-submitted information about outcomes and issues important to patients and caregivers who are affected by HCV.

Patient Input Information

Patient input was contributed by the Canadian Liver Foundation, the Canadian Treatment Action Council, the Hepatitis C Education and Prevention Society, the Pacific Hepatitis C Network, and the Centre Associatif Polyvalent d'Aide Hépatite C. To a large extent, the information for the submissions drew on past consultations regarding other hepatitis C drugs and was gathered through interviews with patients and care givers affected by hepatitis C, health care professionals, and organizations' staff or volunteers, as well as through surveys, social media, meetings with support groups, informal discussions, and a webinar that included patients diagnosed with hepatitis C. The following is a summary of key input from the perspective of the patient groups:

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

- It is a priority to have an alternative course of treatment available for patients who have been previously treated with a DAA therapy without success.
- Patients expect that SOF/VEL/VOX will be very well tolerated and effective for all genotypes, regardless of resistance or the presence of cirrhosis. No ribavirin is required to achieve high cure rates, which distinguishes SOF/VEL/VOX from some other DAA-based regimens used in this difficult-to-treat patient group.
- Patients value the low pill burden and relatively short course of treatment (one pill a day for 12 weeks).

Clinical Trials

The systematic review included two pivotal phase III clinical trials (POLARIS-1 and POLARIS-4). Both trials were randomized and multi-centre. POLARIS-1 was double blind, while POLARIS-4 was open label. POLARIS-1 (N = 415) assessed the efficacy and safety of SOF/VEL/VOX compared with placebo for 12 weeks among patients with genotype 1, 2, 3, 4, 5, or 6 chronic HCV infection who had previously been treated with a DAA regimen containing an NS5A inhibitor. POLARIS-4 (N = 333) assessed the efficacy and safety of SOF/VEL/VOX and SOF/VEL for 12 weeks among DAA-experienced patients with genotype 1, 2, 3, or 4 HCV infection who had not previously been treated with an NS5A inhibitor.

The main limitation of the POLARIS-1 trial was the lack of an active treatment comparator arm consisting of an existing treatment regimen for chronic HCV. The main limitation of the POLARIS-4 trial was the open-label design and a lack of a statistical comparison between treatment arms. Both trials assigned some patients to SOF/VEL/VOX treatment groups non-randomly, primarily because of very small sample sizes in certain genotypes.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following ones: SVR 12, relapse, on-treatment virologic failure, health-related quality of life (HRQoL), and harms.

- SVR 12 was defined as an HCV RNA of less than the lower limit of quantitation (LLOQ) 12 weeks after cessation of treatment.
- Relapse was defined as an HCV RNA ≥ LLOQ during the post-treatment period after having achieved an HCV RNA < LLOQ at end of treatment, as confirmed by two consecutive values or the last available post-treatment measurement.
- On-treatment virologic failure was defined as a breakthrough (an HCV RNA ≥ LLOQ after having previously had an HCV RNA < LLOQ while on treatment, as confirmed with two consecutive values or the last available on-treatment measurement with no subsequent follow-up values); a rebound (a > 1 log10 IU/mL increase in HCV RNA from nadir while on treatment, as confirmed with two consecutive values or the last available on-treatment measurement with no subsequent follow-up values)' or a nonresponse (an HCV RNA persistently ≥ LLOQ through eight weeks of treatment).
- HRQoL was measured using the following instruments:
  - The Short-Form 36-Item Health Survey (SF-36) is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL 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 summary and the mental component summary.
  - The Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV) is 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 zero (worst) to seven (best).
  - Patient-reported symptoms were measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale, which is 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 zero (worst) to 160 (best).
  - The Work Productivity and Activity Impairment (WPAI) questionnaire was used to measure the impact of a disease on work and on daily activities.

- Harms (adverse events, serious adverse events, and withdrawals due to adverse events).

The primary efficacy outcome in both trials was the percentage of patients achieving SVR 12.

Efficacy

- The percentage of patients who achieved SVR 12 was 96.2% (95% CI, 93.1% to 98.2%) in those who received SOF/VEL/VOX for 12 weeks in the POLARIS-1 study. Zero patients in the placebo arm achieved virologic response. The lower bound of the 95% CI (93.1%) exceeded the pre-specified performance goal of 85%, thereby achieving the primary efficacy outcome of the study.
- In the POLARIS-4 study, the percentage of patients who received SOF/VEL/VOX for 12 weeks and achieved SVR 12 was 97.8% (95% CI, 94.5% to 99.4%). The lower bound of the 95% CI (94.5%) exceeded the pre-specified performance goal of 85%. The 12-week treatment group that received SOF/VEL (which was not a Health Canada–approved regimen for the study patient population) did not meet the primary efficacy outcome with a SVR 12 percentage of 90.1% (95% CI, 84.1% to 94.3%) compared with the performance goal of 85%.
- A total of 10 out of 263 patients (3.8%) in the SOF/VEL/VOX 12-week treatment group in the POLARIS-1 study did not achieve SVR 12. Of these, one patient (0.4%) had on-treatment virologic failure (breakthrough) and six patients (2.6%) relapsed.
- In the POLARIS-4 study, in the SOF/VEL/VOX 12-week treatment group, four out of 182 patients (2.7%) did not achieve SVR 12. Of these, one patient (0.5%) relapsed, and three patients (1.6%) were categorized as “Other.” Patients were categorized as “Other” if they did not achieve SVR 12 and did not meet criteria for virologic failure.
- No statistically significant differences were detected between SOF/VEL/VOX and SOF/VEL for the SF-36, the CLDQ-HCV, the FACIT-F, or for the WPAI-HCV instruments. There was a statistically significant difference in favour of SOF/VEL/VOX as compared with placebo for the CLDQ-HCV at final treatment visit. Patient-reported outcomes in the trials were difficult to interpret due to limitations in the data, including the open-label design of POLARIS-4, differences between treatment groups (with the corresponding 95% confidence interval for the treatment difference not estimated), and minimal clinically important differences specific to chronic HCV patient-reported outcomes unknown.

Harms (Safety and Tolerability)

- The majority of patients experienced one or more adverse events, with headache, fatigue, diarrhea, and nausea reported most frequently among those who received SOF/VEL/VOX. In the double-blind placebo-controlled trial, POLARIS-1, 78% and 70% of patients reported adverse events in the SOF/VEL/VOX and placebo groups, respectively. Overall, 77% and 74% of patients in the SOF/VEL/VOX and SOF/VEL12-week groups, respectively, reported an adverse event in the POLARIS-4 study.
- In the POLARIS-1 study, the frequency of serious adverse events (SAEs) was 4.6% in the placebo group at 12 weeks, which was more than double the percentage reported in the SOF/VEL/VOX group (1.9%). One patient in the placebo group experienced an AE that led to interruption of study drug dosing, and four patients (one patient receiving SOF/VEL/VOX and three patients receiving the placebo) permanently discontinued the study drug due to AEs. No patients died during the study.
- In the POLARIS-4 trial, the frequencies of SAEs were similar in the SOF/VEL/VOX 12-week and the SOF/VEL 12-week groups (2.2% and 2.6%, respectively). One patient in the SOF/VEL 12-week group experienced an AE that led to premature discontinuation of the study drug, and one patient in the SOF/VEL/VOX 12-week group died of an illicit drug overdose two days after the last dose of study drug.
- None of the trials were designed to assess longer-term safety or hepatic-related morbidity or mortality, which are important to patients.

Cost and Cost-Effectiveness

The manufacturer submitted a price of $714.29 per tablet, or $60,000 for a 12-week course.

The manufacturer submitted a cost-utility analysis comparing SOF/VEL/VOX to no treatment and SOF/VEL in patients who had previously received SOF without an NS5A inhibitor (i.e., NS5A-naïve patients) based on clinical information from the POLARIS-4 trial, and comparing SOF/VEL/VOX to no treatment in NS5A-experienced patients based on clinical information from the POLARIS-1 trial. The manufacturer used a Markov cohort model where patients started in health states representing initial METAVIR scores with active HCV infection, SVR states, distal consequences of HCV infection, and death. A lifetime time horizon was used, and the analysis was from the perspective of the publicly funded Canadian health care system.

The manufacturer reported that SOF/VEL/VOX is a cost-effective treatment option in HCV patients with genotypes 1 to 6 who are NS5A experienced as well as in genotype 1 to 4 patients who are SOF experienced but NS5A naïve, with SOF/VEL/VOX dominating SOF/VEL (i.e., SOF/VEL/VOX was associated with higher quality-adjusted life-year [QALY] gains and lower overall costs). SOF/VEL/VOX was associated with an incremental cost-utility ratio (ICUR) of $12,000 per QALY compared with no treatment. Results were similar between the genotype 3 and non-genotype 3 populations.

CDR identified the following key limitations with the manufacturer's economic submission:

- The manufacturer combined all genotypes together in the base case. Analysis by genotype was only provided for genotype 3 and non-genotype 3.
- The sample sizes of many subgroups with reported 100% SVR rates were small, and uncertainty in these estimates was not accounted for appropriately.
- Costs for hepatocellular carcinoma health states appear unrealistic and much higher than those observed in the recent CADTH therapeutic review on drugs for the treatment of chronic HCV infection.

CDR could not address most of the limitations identified, either because of the model structure or a lack of clinical information. CDR was only able to conduct a reanalysis that considered alternative costs associated with the hepatocellular carcinoma health state.

The results of the CDR reanalysis did not impact the manufacturer's base case results for non-cirrhotic patients, but in the cirrhotic group, SOF/VEL/VOX was no longer dominant when compared with SOF/VEL but resulted in an ICUR of $923 per QALY. However, as clinical uncertainty could not be addressed in CDR re-analyses given the lack of comparative information for subgroups of interest, the cost-effectiveness results of SOF/VEL/VOX warrant cautious consideration when interpreted, especially for genotypes 2, 4, 5, and 6.

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

December, 13, 2017 Meeting

Regrets:

Two CDEC members did not attend.

Conflicts of Interest:

None