pCODR EXPERT REVIEW COMMITTEE
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the CADTH pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *Procedures for the CADTH pan-Canadian Oncology Drug Review*, which are available on the CADTH website. The Final Recommendation will be posted on the CADTH website once available and will supersede this Initial Recommendation.

Drug: Venetoclax (Venclexta)

Submitted Funding Request: In combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukemia who are fludarabine ineligible

Submitted by: AbbVie Corporation

Manufactured by: AbbVie Corporation

NOC date: April 28, 2020

Submission date: April 17, 2020

Initial Recommendation issued: October 29, 2020

Approximate per patient drug costs, per month (28 days)	Venetoclax costs $7 per 10 mg tablet, $35 per 50 mg tablet, and $70 per 100 mg tablet. At the recommended dose of 400 mg once daily (four 100 mg tablets) following the five-week ramp-up dosing schedule, venetoclax costs $280 per day and per 28-day course: • cycle 1 = $16,532 • cycle 2 = $9,153 • cycle 3 to 6 = $13,318 • cycle 7 to 12 = $7,840.

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends reimbursement of venetoclax (Venclexta) in combination with obinutuzumab (VEN-OBI) for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL) who are fludarabine ineligible if the following condition is met:

- cost-effectiveness improves to an acceptable level

Patients should have previously untreated CLL, be fludarabine ineligible as indicated by either a Cumulative Illness Rating Scale (CIRS) score greater than 6 or a creatine clearance (CrCl) less than 70 mL per minute, require treatment according to the International Workshop on Chronic Lymphoma Leukemia criteria, and have good performance status.

Treatment should be given for a total of 12 months as a finite treatment: for six 28-day cycles in combination with obinutuzumab (OBI) followed by six months of venetoclax (VEN) as a single agent.

pERC made this Recommendation because it was satisfied that there is a net clinical benefit of VEN-OBI compared to chlorambucil plus obinutuzumab

	(CHL-OBI) based on statistically significant and clinically meaningful improvements in progression-free survival (PFS) and minimal residual disease (MRD)-negativity rates three months after treatment completion, a manageable toxicity profile, and maintenance of quality of life (QoL). pERC concluded that VEN-OBI aligns with the following patient values: provides additional treatment choice with finite treatment duration, has manageable side effects, delays disease progression, maintains QoL, and is suitable for patients of advanced age with existing comorbidities. pERC noted that ibrutinib (IBR) would be the standard of care for the subgroup of patients with previously untreated CLL who have a del17p or TP53 mutation, and not CHL-OBI, which was the comparator in the CLL14 trial. pERC considered evidence provided through an indirect treatment comparison (ITC) for this patient population. pERC could not conclude on the comparative efficacy of VEN-OBI compared with IBR due to the lack of robust direct or indirect comparative evidence. pERC concluded that, at the submitted price, VEN-OBI may be cost-effective compared with CHL-OBI based on the direct head-to-head comparative evidence. Limitations with the submitted model suggest that there is uncertainty associated with the economic findings. pERC acknowledged the limitations associated with the comparative evidence derived from the sponsor-submitted indirect comparison; as such, it is uncertain whether VEN-OBI is cost-effective compared with other relevant comparators (e.g., IBR). A price reduction for VEN would improve the likelihood that VEN-OBI is a cost-effective treatment for patients with previously untreated CLL who are fludarabine ineligible.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Decrease Budget Impact** Given that pERC was satisfied that there is a net clinical benefit of VEN-OBI, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of VEN-OBI. pERC noted that a reduction in the price of VEN-OBI would be required to improve the cost-effectiveness to an acceptable level and decrease the predicted budget impact. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

CLL is one of the most common hematologic malignancies, with an incidence of 4.8 cases per 100,000 persons. According to the most recent Canadian statistics, 1,745 Canadians were diagnosed with CLL in 2016, and 611 died from this disease in 2017. There are several treatment options for patients with previously untreated symptomatic CLL who are fludarabine ineligible. The standard of care is CHL-OBI; bendamustine plus rituximab (BEN-RIT) is also an option in this setting. Patients with the chromosome 17p deletion (del17p) are treated with B-cell receptor inhibitors such as IBR. pERC noted that acalabrutinib with or without OBI is currently under review at CADTH for the treatment of patients with previously untreated CLL for whom a fludarabine-based regimen is inappropriate. pERC agreed with the Clinical Guidance Panel (CGP) and registered clinicians that there is a continued need for treatment options for CLL patients who are fludarabine ineligible that are effective and delay disease progression, have a manageable toxicity, and improve QoL.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated the results of one international, open-label, phase III, randomized trial (CLL14), which evaluated the efficacy and safety of VEN-OBI compared to CHL-OBI for first-line treatment of CLL patients with coexisting conditions. pERC noted that CHL-OBI is a relevant comparator for patients without del17p or tumour protein 53 (TP53) mutations, whereas IBR would be the relevant comparator for patients with del17p or TP53 mutations. pERC considered that the difference in PFS, the primary outcome in the CLL14 trial, was statistically significant and clinically meaningful in favour of VEN-OBI. Improvements in PFS were seen across most subgroups. pERC noted that the treatment benefit of VEN-OBI was observed across all secondary efficacy outcomes, which included independent review committee (IRC)–assessed PFS, and the following outcomes evaluated three months after treatment completion: MRD in bone marrow, complete response rate, MRD in peripheral blood, MRD in bone marrow of patients with a complete response (CR), MRD in peripheral blood in patients with a CR, and overall response rate, except for overall survival (OS). pERC noted that the results for OS were immature at the latest data cut-off point and therefore the OS analyses were considered descriptive in nature. Overall, pERC agreed with the CGP and the registered clinicians that PFS is a clinically meaningful outcome in patients with CLL.

pERC deliberated the toxicity profile of VEN-OBI and noted that the incidence and severity of adverse events (AEs) were broadly similar between the VEN-OBI and CHL-OBI groups. pERC noted that the incidence of tumour lysis syndrome (TLS), which was an AE of special interest, was low in the trial, with a similar incidence in the VEN-OBI and CHL-OBI groups. pERC also noted that all occurrences of TLS in the VEN-OBI group occurred during the administration of OBI only — prior to starting VEN. Overall, pERC agreed with the CGP that VEN-OBI has a manageable safety profile. pERC discussed the patient-reported outcome (PRO) data from the CLL14 trial. pERC noted that overall QoL was similar between groups and did not show a negative effect from VEN-OBI compared with CHL-OBI. Therefore, pERC considered that patients treated with VEN-OBI maintained QoL during treatment and during the follow-up period.

Overall, pERC concluded that VEN-OBI compared with CHL-OBI has a net clinical benefit based on statistically significant and clinically meaningful improvements in PFS and MRD-negativity rates three months after treatment completion, a manageable toxicity profile, and maintenance of QoL.

pERC deliberated upon the input received from one joint submission from two patient advocacy groups, Lymphoma Canada (LC) and Chronic Lymphocytic Leukemia Patient Advocacy Group (CLLPAG), and noted that patients value treatment options with minimal side effects, better disease management, delayed progression, increased survival, increased QoL, and have proven efficacy in treating a range of patients, including those who have poor prognostic factors and those of advanced age with existing co-morbidities. pERC considered that the majority of patients with direct experiences with VEN-OBI indicated that VEN-OBI was able to manage all their CLL or small lymphocytic leukemia (SLL) disease symptoms, that the side effects experienced from VEN-OBI were reported to have little impact on their QoL, and that aspects of daily activities were mostly unchanged or improved due to treatment. pERC agreed that VEN-OBI aligns with patient values in that it offers an additional treatment choice with a finite treatment duration, has

manageable side effects, and delays disease progression. pERC acknowledged that patients also valued improvement in QoL. Although the CLL14 trial did not demonstrate an improvement in QoL with VEN-OBI, pERC considered that QoL was maintained in patients treated with VEN-OBI.

In addition to the CLL14 trial, pERC also deliberated the results of submitted ITCs that aimed to estimate the relative effectiveness of VEN-OBI with other relevant treatments for this patient population and the subgroup of patients with del17p or TP53 mutations. Overall, results demonstrated that VEN-OBI was favoured over most treatments in CLL patients who are fludarabine ineligible, and that there were no statistically significant differences between VEN-OBI and IBR in most analyses for the del17p or TP53 mutation population. However, pERC acknowledged the limitations of all the ITCs noted by the CADTH Methods Team and agreed with its concerns regarding heterogeneity across the study designs and populations; the exclusion of acalabrutinib, which is a potentially relevant comparator; and lack of evidence for QoL and safety outcomes. Therefore, pERC agreed with the CGP and CADTH Methods Team and concluded there is uncertainty with respect to the comparative effectiveness of VEN-OBI to other relevant treatments for patients with CLL.

pERC deliberated on the cost-effectiveness of VEN-OBI in the reimbursement request population (i.e., patients with CLL who are previously untreated and are fludarabine ineligible) versus the submitted comparators (IBR, CHL-OBI, chlorambucil plus rituximab [CHL-RIT], BEN-RIT). pERC noted there were limitations with the ITC used to inform the economic analysis that limited the interpretation of the results of the sequential analysis. As such, pERC concluded that the cost-effectiveness of VEN-OBI compared with treatments such as IBR and BEN-RIT is unknown. Given the existing clinical evidence, pERC considered that the comparison of VEN-OBI to CHL-OBI based on the extrapolated CLL14 trial data represented a more appropriate comparison; however, the Committee acknowledged that the economic results for this scenario were uncertain given the identified limitations with the submitted model. Given the level of uncertainty associated with the economics findings, pERC considered that a price reduction for VEN is required to improve the likelihood that VEN-OBI is a cost-effective treatment in current practice. pERC noted the evidence was only applicable to the reimbursement request population, and that the lack of clinical data in the broader Health Canada population highlights that the cost-effectiveness in the broader Health Canada-indicated population is unknown.

The Committee deliberated on the input from PAG regarding factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from one joint submission from two patient advocacy groups, LC and CLLPAG
- input from one individual clinician and one joint clinician input on behalf of two clinicians from Cancer Care Ontario
- input from pCODR's PAG.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of venetoclax in combination with obinutuzumab compared with the standard of care in Canada for patients with previously untreated CLL who are fludarabine ineligible.

Studies included: One open-label, phase III, randomized trial (CLL14)

The CADTH systematic review included one international, open-label, phase III, randomized, active-controlled superiority trial (CLL14) that evaluated the efficacy and safety of VEN-OBI compared to CHL-OBI for first-line treatment of CLL patients with coexisting conditions. The trial was conducted at 196 sites across 21 countries, which included 13 patients from Canada. Patients were randomized in a 1:1 ratio to receive either VEN-OBI or CHL-OBI. No crossover was permitted between treatment groups. The trial was open-label; however, the sponsor and an IRC were blinded to the treatment arms. Eligible patients were 18 years of age or older, had previously untreated CLL that required treatment, and either a CIRS score greater than 6 or a CrCl less than 70 mL per minute. Patients were randomized to receive either VEN-OBI or CHL-OBI for 12 cycles of 28 days. No crossover was permitted between treatment groups.

Patient populations: Baseline characteristics well-balanced

Overall, the baseline characteristics in the trial arms were well-balanced. A total of 432 patients were randomly assigned to receive either VEN-OBI (n = 216) or CHL-OBI (n = 216). The median age was 72 years (range = 41 to 89), with 33.3% and 36.1% of patients aged 75 years or older in the VEN-OBI group and CHL-OBI group, respectively. Most patients were male (67.6% in VEN-OBI group; 66.2% in CHL-OBI group), and most were categorized as "intermediate" risk of TLS (64.4% in VEN-OBI group; 68.1% in CHL-OBI group). The median CIRS score for all trial participants was 8 (range = 0 to 28). Median CIRS scores were slightly higher in the VEN-OBI group compared with the CHL-OBI group (9 versus 8), with 86.1% and 81.9% of patients having a CIRS score greater than 6 in the VEN-OBI group in the CHL-OBI group, respectively. The proportion of patients with CrCl less than 70 mL per minute was slightly higher in the VEN-OBI group compared with the CHL-OBI group (59.5% versus 55.4%). The percentage of patients in the cytogenetic subgroups were balanced for the VEN-OBI group compared with the CHL-OBI group: deletion in 17p = 8.5% versus 7.3%, deletion in 11q = 18.0% versus 19.7%, trisomy 12 = 18.0% versus 20.7%, no abnormalities = 25.0% versus 21.8%, and deletion in 13q alone = 30.5% versus 30.6%. Most patients in both groups had unmutated immunoglobulin heavy chain variable region genes (IGHV) (VEN-OBI: 60.5%; CHL-OBI: 59.1%), and unmutated TP53 (VEN-OBI: 88.9%; CHL-OBI: 91.7%).

Key efficacy results: Clinically meaningful improvements in PFS in favour of VEN-OBI; OS data immature

The key efficacy outcome deliberated on by pERC was investigator-assessed PFS. The secondary efficacy outcomes included IRC-assessed PFS, OS, and the following outcomes evaluated three months after treatment completion: MRD in bone marrow, complete response rate, MRD in peripheral blood, MRD in bone marrow of patients with a CR, MRD in peripheral blood in patients with a CR, and overall response rate. pERC noted that, as of the primary data cut-off date, investigator-assessed PFS was statistically significant longer in the VEN-OBI group compared with the CHL-OBI group ($P < 0.0001$). Although median PFS had not been reached in either group, results of the primary analyses demonstrated a hazard ratio

(HR) of 0.35 (95% confidence interval [CI], 0.23 to 0.53; P < 0.0001). The PFS benefit for VEN-OBI was consistently demonstrated at the updated data cut-off date (HR = 0.31; 95% CI, 0.22 to 0.44; P < 0.0001).

Overall, the results of the key secondary efficacy outcomes were consistent with the primary outcome: the results demonstrated an improvement on VEN-OBI compared with CHL-OBI. At both the August 17, 2018, and the August 23, 2019, data cut-offs, the OS data were immature and median OS was not estimable for either treatment group. As of the primary data cut-off date, 37 patients had died (VEN-OBI group: 20 patients; CHL-OBI group: 17 patients) corresponding to an HR of 1.24 (95% CI, 0.64 to 2.40; P = 0.5216). At 24 months, the Kaplan-Meier estimate of the percentage of patients still alive was 91.8% (95% CI, 88.1% to 95.5%) in the VEN-OBI group and 93.3% (95% CI, 90.0% to 96.7%) in the CHL-OBI group. At the time of the August 23, 2019, data cut-off, 54 patients had died (27 patients in each treatment group) corresponding to an HR of 1.03 (95% CI, 0.60 to 1.75; P = 0.9210).

Patient-reported outcomes: QoL is maintained on both VEN-OBI and CHL-OBI treatment

In the CLL14 trial, PROs were assessed with the M.D. Anderson Symptom Inventory (MDASI)-CLL and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30). For the MDASI-CLL, baseline scores were comparable for the VEN-OBI group versus the CHL-OBI group: CLL symptoms (1.6 ± 1.3 versus 1.5 ± 1.2), core cancer symptoms (1.8 ± 1.7 versus 1.5 ± 1.4), and symptom interference (2.3 ± 2.3 versus 2.1 ± 2.3). No significant improvement or deterioration to the score was demonstrated throughout treatment and the follow-up period. For the EORTC QLQ-C30, baseline scores were comparable for the VEN-OBI group versus the CHL-OBI group: physical functioning (76.9 ± 19.4 versus 75.9 ± 20.1), role functioning (72.6 ± 26.9 versus 73.6 ± 27.86), and Global Health Status/Quality of Life (GHS/QoL) (60.3 ± 20.5 versus 63.6 ± 21.0). The most severe symptoms at baseline were (listed as VEN-OBI versus CHL-OBI) dyspnea (24.8 ± 27.76 versus 21.3 ± 25.6), fatigue (39.2 ± 24.7 versus 35.8 ± 23.3), insomnia (30.8 ± 30.5 versus 26.9 ± 29.0), pain (18.4 ± 25.6 versus 16.8 ± 22.1), appetite loss (15.6 ± 26.7 versus 14.7 ± 23.6), and constipation (12.8 ± 23.7 versus 10.9 ± 20.9). Baseline physical and role functioning were maintained throughout treatment and the follow-up period with no clinically meaningful improvement or deterioration to the scores. Patients showed an improvement of the GHS/QoL score by at least 8 points at cycle 3 in the VEN-OBI group and at cycle 8 in the CHL-OBI group. Insomnia and fatigue scores also showed an improvement starting at cycle 3 in the VEN-OBI group and at cycles 4 and 6 in the CHL-OBI group.

Limitations: IBR is considered the standard of care for previously untreated CLL patients with a del17p or TP53 mutation

The main limitations outlined by the Methods team and discussed by pERC were the following:

- At the time of both the August 17, 2018, and the August 23, 2019, data cut-offs, the OS data were immature and the median OS was not estimable for either treatment group; therefore, the magnitude of long-term survival benefit is currently unknown. Although patient crossover upon disease progression was not permitted in the trial, survival data will be confounded by the use of post-trial treatments. Of note, OS was listed last in the hierarchical order, which may potentially limit the power to analyze this outcome.
- The comparator of the CLL14 trial was CHL-OBI; however, the CGP noted that IBR is considered the standard of care for the subgroup of patients with previously untreated CLL who are unfit and have a del17p or TP53 mutation. Although ITCs were conducted to investigate the comparison of VEN-OBI to IBR in these patients, many limitations of these analyses were identified. Thus, results were interpreted with caution.
- Several other secondary efficacy analyses were conducted (i.e., DOR, EFS, and time to new anti-leukemic treatment) as were multiple subgroup analyses. The results of these analyses should be interpreted as exploratory and hypothesis generating because the CLL14 trial was not designed or powered to test specific hypotheses in these analyses.

Safety: Manageable safety profile with study protocol ramp-up dosing scheme

At least one AE of any grade was reported in 94.3% of patients in the VEN-OBI group and in 99.5% of patients in the CHL-OBI group, with most AEs being blood and lymphatic system disorders. The most common grade 3 or 4 AEs in the VEN-OBI group versus the CHL-OBI group were neutropenia (52.8% versus 48.1%), thrombocytopenia (13.7% versus 15.0%), and anemia (8.0% versus 6.5%). The incidence of TLS was lower in the VEN-OBI group compared with the CHL-OBI group (0.5% versus 1.9%), and all occurrences of TLS in the VEN-OBI group occurred during the OBI-only period before starting VEN. During treatment, five fatal AEs occurred in the VEN-OBI group, and four occurred in the CHL-OBI group. Two of the fatal AEs in the VEN-OBI group occurred in patients who received only OBI. After treatment, 11 fatal AEs occurred in

the VEN-OBI group, and four occurred in the CHL-OBI group. As of the primary data cut-off, Richter transformation was reported in two patients in the VEN-OBI group and in one patient in the CHL-OBI group, with one additional transformation reported in the CHL-OBI group at the updated data cut-off. Second primary cancers were reported in 13.7% of patients in the VEN-OBI group and in 10.3% of patients in the CHL-OBI group as of the primary data cut-off, as well as an additional seven patients experiencing second primary malignancies in the VEN-OBI group at the time of the updated data cut-off. Although a higher percentage of patients in the VEN-OBI group experienced second primary malignancies, the majority of occurrences were squamous cell carcinomas. This type of cancer is not unexpected in CLL patients, and there is no evidence to suspect a higher frequency of treatment-related malignancies in either study group.

Need and burden of illness: Need for additional treatment options

CLL is one of the most common hematologic malignancies, with an incidence of 4.8 cases per 100,000 persons; 1,745 Canadians were diagnosed with CLL in 2016, and 611 died from this disease in 2017 according to the most recent available Canadian statistics. The majority of persons with CLL are asymptomatic and diagnosed because of the finding of an elevated white blood cell count.

For first-line treatment of patients with CLL who require treatment and are in good health and younger than 65 years, fludarabine plus cyclophosphamide plus rituximab (FCR) is standard in most provinces in Canada. However, patients treated with fludarabine have a higher rate of severe infection and neutropenia; therefore, patients older than 65, or those who are not considered fit enough to receive FCR, may derive benefit from several less-intensive regimens. CHL-OBI is a standard agent for older patients or those with significant comorbidities. BEN-RIT may also be appropriate for older patients or those with limited comorbidities. For management of patients with CLL with abnormalities in del17p or TP53, IBR is approved as initial therapy for patients with del17p CLL and publicly funded in almost all provinces. Acalabrutinib is also currently under review by CADTH for a similar indication: "with or without obinutuzumab, for the treatment of patients with previously untreated CLL for whom a fludarabine-based regimen is inappropriate."

Registered clinician input: VEN-OBI may replace CHL-OBI as first-line therapy

Input from one individual clinician and one joint clinician input on behalf of two clinicians were provided for the review of VEN-OBI for patients with previously untreated CLL: one from an individual oncologist from Ontario and one joint input from clinicians from Cancer Care Ontario. Currently available treatments for patients with CLL ineligible for fludarabine-based regimens were stated to be CHL-OBI, bendamustine ± rituximab, or IBR monotherapy; the funding of these treatments was stated to vary across jurisdictions in Canada. Nearly all patients who are ineligible for fludarabine-based regimens and are currently eligible for CHL-OBI were considered to be eligible for VEN-OBI by clinicians; most eligible patients were acknowledged to be elderly and with significant comorbidities. Eligibility criteria from the CLL14 trial were considered reasonable for implementation in practice, and the use of a CIRS score greater than 6 or CrCl less than 70 mL per minute to categorize "unfit" CLL patients was stated to be standard in clinical trials and in clinical practice.

Both clinician inputs acknowledged that trial data showed that treatment with VEN-OBI is superior to CHL-OBI and may replace CHL-OBI as first-line therapy for eligible patients. The individual clinician noted that IBR may place some patients at high risk for cardiac or bleeding complications, and that those patients who are high risk with del17p or TP53 mutations may benefit from treatment with VEN-OBI instead of IBR. However, the clinicians from the joint input expressed that VEN-OBI would likely not replace IBR for subgroups of patients with del17p, TP53, and IGHV mutation status. Although the CLL14 trial did not address the possibility of re-treatment with VEN-OBI or venetoclax plus rituximab, the individual clinician highlighted the MURANO trial, which may suggest that patients can continue to respond to venetoclax because re-treatment was permitted in the trial. If VEN-OBI were to receive funding, IBR was suggested as a possible therapy in the second line or beyond. The individual clinician also suggested acalabrutinib as another treatment option for patients in the second line. Of note, acalabrutinib in a similar indication is currently under CADTH review. At relapse after second line therapy, idelalisib plus rituximab, chemoimmunotherapy, or entry into a clinical trial were suggested as possible treatment options.

PATIENT-BASED VALUES

Experience of patients with CLL: Fatigue a key symptom; other symptoms included enlarged lymph nodes and shortness of breath due to anemia

One joint submission from two patient advocacy groups, LC and CLLPAG, was provided for the treatment of patients with previously untreated CLL who are fludarabine ineligible. Fatigue (83%), frequent infections (27%), enlarged lymph nodes (23%), and shortness of breath due to anemia (20%) were commonly reported disease symptoms affecting patients' QoL on an ongoing basis. IBR was the most commonly reported previous therapy (67%). Commonly reported side effects related to treatments included fatigue, nausea, reduced blood counts, diarrhea, and frequent infections; fatigue, nausea and frequency of infections were reported to be most difficult to tolerate. Oral treatments were reported to less negatively impact patients' QoL compared to IV therapies. Many patients (48%) reported a need for treatments with better disease symptom management.

Patient values on treatment: Treatment option with minimal side effects, better disease management, delayed progression, increased survival, and increased QoL

A total of 33 patients reported having experience with VEN-OBI as first-line treatment. At survey completion, most patients either completed or were still receiving VEN-OBI treatment. Enlarged lymph nodes (82%), fatigue (76%), and an enlarged spleen (58%) were the most commonly managed disease symptoms as a result of VEN-OBI. Almost two-thirds of patients (61%) indicated that VEN-OBI was able to manage all their CLL or SLL disease symptoms. Fatigue (30%) and shortness of breath (12%) were symptoms patients reported that VEN-OBI was not able to manage. Commonly reported side effects from VEN-OBI included muscle or joint pain (45%), neutropenia (42%), and thrombocytopenia (30%). The side effects experienced from VEN-OBI were reported to have little impact on patients' QoL; aspects of daily activities were mostly unchanged or improved due to treatment. From a patient's perspective, having a choice in treatment options with proven efficacy for patients with poor prognostic factors and those of advanced age with existing co-morbidities was considered very important. Overall, patients value treatments with minimal side effects, that are able to better manage disease symptoms, have increased effectiveness resulting in delayed disease progression and increased survival, and improve QoL.

ECONOMIC EVALUATION

Venetoclax is supplied as an oral tablet available in 10 mg, 50 mg, and 100 mg strengths, at a cost of $7, $35, and $70 per tablet, respectively. Venetoclax, when used in combination with obinutuzumab, is taken using a specified dose ramp-up approach. Venetoclax is taken for a fixed treatment duration of 12 cycles; obinutuzumab is administered intravenously for six cycles. The drug acquisition cost of VEN-OBI over a treatment course of 12 cycles is $125,996 or an average of $10,500 per 28-day cycle (range = $7,840 to $16,532).

The sponsor submitted a cost-utility analysis comparing costs and quality-adjusted life-years for VEN-OBI with currently available treatment options for all previously untreated CLL patients (CHL-OBI, BEN-RIT, CHL-RIT, IBR, and FCR). The target population for the base case aligns with the Health Canada–approved indication. A scenario analysis was performed for treatment of previously untreated CLL patients who are unfit or ineligible for fludarabine based treatment on the sponsor's reimbursement request. This latter population was based on the CLL14 trial. The sponsor considered the same clinical data for VEN-OBI in both patient populations. Costs and quality-adjusted life-years were modelled over a 10-year time horizon from a public health care payer perspective. The sponsor submitted a partitioned survival model consisting of three health states: progression-free, post-progression, and death. All patients were assumed to be progression-free on model entry; over time, the proportion of patients with progressed disease was estimated as the difference between the proportion of living patients (estimated from the OS curve) and the proportion of progression-free patients (estimated from the PFS curve). PFS and OS curves for VEN-OBI and CHL-OBI were derived from the CLL14 trial and extrapolated using standard parametric distributions. Comparative efficacy for additional comparators versus VEN-OBI was derived using an ITC. Data were extrapolated such that PFS was always lower than or equal to OS, and OS was always lower than or equal to age-adjusted background mortality for the general population. Time on treatment and time to next treatment were also derived from the trials included in the ITC. Health state utility values were derived from published NICE health technology assessments. In the sponsor's base case, VEN-OBI dominated all other treatments.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- The clinical evidence for VEN-OBI was derived from a population reflective of the reimbursement request population. The CGP considered these data not generalizable to the broader Health Canada–indicated population. Due to this gap in the clinical evidence, the cost-effectiveness of VEN-OBI in the Health Canada population is unknown.
- The comparative clinical efficacy of VEN-OBI versus the comparators assessed in the ITC is uncertain. The fixed effects ITC was identified to have substantial heterogeneity in the populations included, differences in effect modifiers, and in the design of included studies. The PFS HRs resulting from the ITC — the key driver of the model results — were deemed to have questionable face validity; the CGP agreed that the HRs were higher than expected in clinical practice, although the magnitude of difference was unclear.
- CADTH also identified limitations relating to how the ITC data were applied in the model. The decision to apply HRs that are dependent on the VEN-OBI curves restrains the explanatory power of the model and underestimates the variability of the potential treatment outcomes. These constraints tend to bias the results in accordance with the HRs reported from the ITC.
- The model assumptions used to determine time to next treatment differed between treatments and were associated with uncertainty given the lack of long-term data to support these assumptions.

Given the lack of clinical evidence for VEN-OBI in previously untreated CLL patients who are fludarabine-eligible, the cost-effectiveness of VEN-OBI in this population is unknown. CADTH addressed several minor limitations that were identified, including corrections to the standard error estimates and pricing of rituximab, and revisions to terminal care costs. However, due to the limitations identified with the comparative clinical evidence and model logic, CADTH was unable to determine a base-case analysis. CADTH did consider a series of scenario analyses that assessed alternate PFS and OS HRs, as well alternate assumptions regarding post-progression costs and time to next treatment.

Although CADTH revisions, based on best available data, indicated that VEN-OBI remained dominant compared with all comparators and reported similar findings to the sponsor's base case; limitations with the submitted model logic (as well as other identified limitations) could not be addressed. CADTH scenario analyses highlighted the sensitivity of the results to alternate assumptions for the PFS HRs and subsequent treatment assumptions. Although CADTH scenario analyses indicated that VEN-OBI may be cost-effective based on some scenarios regarding the long-term effects of VEN-OBI, the limitations with the model further add to the uncertainty of the cost-effectiveness of VEN-OBI.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Submitted budget impact analysis is associated with substantial uncertainty

The sponsor's budget impact analysis was associated with notable limitations, including uncertainty associated with the estimation of the population size, lack of clinical evidence for the Health Canada-indicated population, and market share displacement assumptions. CADTH reanalyses suggested the estimated budget impact for VEN-OBI may range from $8,087,572 to $18,805,174 over three years in the population aligned with the reimbursement request based on the submitted and publicly available prices.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Michael Crump, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Health Economist
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Maureen Trudeau, who did not vote due to her role as pERC Chair
- Dr. W. Dominika Wranik, who was not present for the discussion and deliberation for this review.

Avoidance of conflicts of interest

All members of the CADTH pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of venetoclax in combination with obinutuzumab for the treatment of adult patients with previously untreated CLL who are fludarabine ineligible, through their declarations, no pERC members had a real, potential, or perceived conflict; therefore, based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the CADTH website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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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.

APPENDIX 1: CADTH pCODR RESPONSES TO PAG IMPLEMENTATION QUESTIONS

PAG implementation questions	pERC Recommendation
Eligible patient population	
PAG is seeking clarity on whether the following patients would be eligible for treatment with VEN-OBI in the first-line setting: • patients with a score lower than 6 on the CIRS	• The eligibility inclusion criteria for the CLL14 trial specified patients with a CIRS score > 6 OR a CrCl of < 70 mL/min, there would have been patients enrolled with CIRS score ≤ 6 (as long as their CrCl was < 70 mL/min). pERC agreed with the CGP that patients with a CIRS score < 6 would be eligible for VEN-OBI if they were considered fludarabine ineligible.
• CD20-negative CLL	• The trial publication indicated the trial included patients who had CD20+ CLL, however the sponsor indicated that this was not part of the patient eligibility requirements. pERC noted that the CGP felt these patients would be unlikely to respond to the OBI portion of VEN-OBI treatment. pERC therefore noted that there is currently insufficient evidence to make an informed recommendation on the use of VEN-OBI for patients with CD20-negative CLL.
• known CNS lymphoma or leukemia, or known prolymphocytic leukemia, or history of (or currently suspected) Richter syndrome	• pERC agreed with the CGP that patients with these high-risk comorbidities (known CNS lymphoma or leukemia, or known prolymphocytic leukemia or history of, or currently suspected, Richter syndrome) were excluded from the CLL14 trial and there is currently insufficient evidence to make an informed recommendation on the use of VEN-OBI for these patients.
• patients with or without high-risk cytogenetic or mutational features (e.g., 17p deletion, TP53 mutation)	• Patients with and without high-risk cytogenetic or mutational features (e.g., 17p deletion, TP53 mutation) were included in the CLL14 trial. pERC agreed with the CGP that it was reasonable for these patients to be eligible for VEN-OBI.
• patient with SLL.	• Patients with SLL were not included in the CLL14 trial. Although there is no direct evidence to support the use of VEN-OBI in SLL patients, treatments for CLL and SLL are often considered the same; therefore, pERC agreed with the CGP that the results would be applicable to patients with SLL.
Implementation factors	
The dosing schedule for VEN-OBI is for a fixed duration of 48 weeks. PAG is seeking clarity on treatment duration. • For patients who do not experience progression, whether there are instances where these patients should be treated beyond the 48 weeks of treatment.	• pERC agreed with the CGP that there is no evidence to support the use of VEN-OBI beyond the 48 weeks of treatment in patients who do not experience progression. pERC agreed with the CGP that patients should be treated for the equivalent of 48 weeks (i.e., if treatment was paused and then resumed, the total time of treatment should equal 48 weeks).

• For patients who have completed the 48 weeks of treatment, whether these patients should be re-treated with VEN-OBI upon progression.	• pERC agreed with the CGP that there is no evidence to support re-treatment with VEN-OBI upon progression.
Sequencing and priority of treatment	
PAG is seeking guidance on the appropriate place in therapy of VEN-OBI and overall sequencing of all treatments available for CLL and SLL. In particular, PAG would need information on the following aspects: • clinical scenarios justifying preferential use of VEN-OBI, acalabrutinib, or IBR in high-risk (del17p) patients, and of VEN-OBI, acalabrutinib, or CHL-OBI in FCR-ineligible patients	• pERC agreed with the CGP that there is currently no evidence to justify preferential use of VEN-OBI, acalabrutinib, or IBR in high-risk (del17p) patients, and of VEN-OBI, acalabrutinib, or CHL-OBI in FCR-ineligible patients.
• use of venetoclax with rituximab (including subcutaneous formulation) for first-line treatment, given that this combination can be used in the RR CLL space	• pERC agreed with the CGP that there is currently no evidence to support the use of venetoclax with rituximab for first-line treatment. However, pERC acknowledged that the CGP noted that physicians would be unlikely to use venetoclax in a first-line setting and again in an RR CLL setting.
• sequencing of VEN-OBI, BEN-RIT, CHL-OBI, IBR, idelalisib plus rituximab, and acalabrutinib from newly diagnosed CLL to RR CLL	• pERC was unable to make an informed recommendation on the optimal sequencing of VEN-OBI with other therapies in CLL/SLL because current data do not inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of VEN-OBI and noted that a national approach to developing evidence-based clinical practice guidelines would be of value.
• since venetoclax treatment has a fixed duration, PAG seeks guidance on the appropriateness and timing of re-treatment with venetoclax (either venetoclax, VEN-OBI, or venetoclax with rituximab) after prior VEN-OBI.	• pERC agreed with the CGP that that there is currently no evidence to determine the appropriateness and timing of re-treatment with venetoclax after prior VEN-OBI use.

BEN-RIT = bendamustine plus rituximab; CGP = Clinical Guidance Panel; CHL-OBI = chlorambucil plus obinutuzumab; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukemia; CNS = central nervous system; FCR = fludarabine plus cyclophosphamide plus rituximab; IBR = ibrutinib; PAG = Provincial Advisory Group; pCODR = pan-Canadian Oncology Drug Review; RR = relapsed or refractory; SLL = small lymphocytic lymphoma; VEN-OBI = venetoclax plus obinutuzumab.