pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL 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.

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Venetoclax (Venclexta) **Submitted Reimbursement Request:** As monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-cell receptor inhibitor (BCRi)	
Submitted By: AbbVie Corporation	**Manufactured By:** AbbVie Corporation
NOC Date: September 30, 2016	**Submission Date:** July 10, 2017
Initial Recommendation: November 30, 2017	**Final Recommendation:** March 02, 2018

Drug Costs	
Approximate per Patient Drug Costs, per Month (28 Days)	Venetoclax (Venclexta) costs $6.80 per 10 mg, $33.99 per 50 mg, and $67.99 per 100 mg. Ramp-up dose: $62.89 per day and $1,760.88 per 28-day course. Subsequent doses: $271.95 per day and $7,614.60 per 28-day course.

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) conditionally recommends the reimbursement of venetoclax (Venclexta) for patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-cell receptor inhibitor (BCRi) only if the following condition is met:

- an improvement of cost effectiveness in the form of a substantial price reduction until more robust clinical data are made available for a future reassessment.

If the aforementioned condition cannot be met, pERC does not recommend its reimbursement. Patients should have a good performance status and treatment should be continued until disease progression or unacceptable toxicity up to a maximum of 2 years.

pERC made this recommendation because the Committee considered that there may be a net clinical benefit of venetoclax. pERC agreed there is an unmet need in this patient population as there are no other effective therapeutic options for end-of-line treatment and the clinical course of CLL that is relapsed or refractory to a BCRi is aggressive. pERC also considered the improvements in one-year overall survival and progression-free survival rates as demonstrated in the pivotal M14-032 trial and supported by historical data to be meaningful. pERC also considered that the side effect profile of the drug is manageable.

pERC concluded that venetoclax aligns with patient values because it is a new treatment option with demonstrated disease control,

	improvements in some aspects of quality-of-life (QoL) and ease of use as an oral therapy. However, because of the non-randomized, non-comparative phase II study design, there was considerable uncertainty about the magnitude of the clinical benefit and, therefore, about the incremental cost-effectiveness of venetoclax. This uncertainty led to a wide range of incremental cost-effectiveness estimates. Therefore, venetoclax could not be considered cost-effective at the submitted price. pERC also highlighted that the potential budget impact of venetoclax is likely underestimated and could be substantial.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC concluded that there may be a net clinical benefit of venetoclax in patients with CLL who have received at least one prior therapy and who have failed a BCRi, jurisdictions should consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of venetoclax to an acceptable level. **Ensuring Evidence-Based Clinical Effectiveness and Cost-effectiveness** pERC noted that the estimated completion date for the M14-032 trial is at the end of 2018. Given the considerable uncertainty in the magnitude of clinical benefit and cost-effectiveness, jurisdictions should consider a time-limited reimbursement of venetoclax, with a reassessment of the efficacy, safety, and cost-effectiveness when the final results of the M14-032 study or other more robust data are available from the submitter. pERC noted that this approach would help facilitate the equitable and timely access to promising treatments for patients while ensuring that treatments considered for public reimbursement adhere to a level of rigour that sufficiently demonstrates effectiveness, safety, and cost-effectiveness. **Factors Affecting Budget Impact and Adoption Feasibility** pERC noted that the budget impact of venetoclax is likely to be high as there is a large prevalent population with CLL that is relapsed or refractory to a BCRi. pERC also noted that the budget impact analysis (BIA) only considered patients who are relapsed or refractory to prior ibrutinib; however, it is anticipated that most patients qualifying for treatment with venetoclax will be intolerant to prior ibrutinib. Given that this population of patients with intolerance to ibrutinib was not considered in the BIA, pERC agreed with the Economic Guidance Panel (EGP) that the submitted BIA is likely substantially underestimated. **Monitoring for Tumor Lysis Syndrome** pERC acknowledged that TLS is now well managed with appropriate triaging of patients and properly scheduled bloodwork including blood chemistry. pERC however noted that this would be best handled by centers with pharmacies able to appropriately manage potential toxicities during the ramp-up phase of treatment. Notwithstanding this, pERC noted there may be some patients at high risk for TLS who will need to be managed in hospital.

SUMMARY OF pERC DELIBERATIONS

CLL is a common leukemia with a long natural history. Each year, approximately 2,400 Canadians are diagnosed with CLL and 650 die from it, with a median age at diagnosis of 72 years. There is currently no consensus on treatment options for patients who have previously received treatment with ibrutinib and/or idelalisib and who have relapsed on treatment or have experienced progression after discontinuation of either of these agents. Available agents for use may include single-agent rituximab or rituximab plus high-dose methylprednisolone (HDMP). In these patients with relapsed or refractory disease, the median overall response rates are poor (20% to 50%), and PFS has typically been less than six months. The outlook for some subgroups of patients with CLL, particularly those who have high-risk disease — chromosome 17p13.1 deletion, or del(17p) — is especially poor, as the presence of these mutations is associated with resistance to standard chemoimmunotherapy, and effective agents with activity in this biologically aggressive subgroup are needed. pERC therefore concluded that there is a need for effective treatment options in this patient population and particularly in those with the del(17p) mutation.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

The pCODR systematic review included one non-randomized, non-comparative, open-label, phase II trial (M14-032) examining the efficacy and safety of venetoclax in patients with CLL who have previously received treatment with ibrutinib and/or idelalisib and who have relapsed on treatment or have experienced progression after discontinuation of either of these agents. During deliberation on the Initial Recommendation, pERC had considered that the M14-032 trial demonstrated promising biological activity based on improvements in objective response rate (ORR). However, the Committee was not satisfied that the available evidence demonstrated a net overall clinical benefit of treatment compared with available treatments. At the time the Committee was unable to draw a conclusion on the comparative effectiveness of venetoclax in this patient population because of the absence of mature progression-free survival (PFS) and overall survival (OS) data, the interim nature of the available data, the feasibility of conducting a randomized trial in this disease setting, the short trial follow-up, and low rates of complete responses to treatment. pERC had also noted that the results of the Mato et al. retrospective analyses were promising, but prone to several forms of bias and must be interpreted with caution. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the submitter, registered clinicians, and two patient advocacy groups and clarification from the pCODR Clinical Guidance Panel (CGP) on the interpretation of the available evidence. pERC recognizes that the Committee's decisions must be equitable, transparent, timely, and accountable to patients, health care funders, and the public while ensuring that treatments considered for public reimbursement adhere to a level of rigour that sufficiently demonstrates effectiveness, safety, and cost-effectiveness. In light of the extensive feedback received, pERC had substantive re-deliberations on the robustness of the efficacy and safety outcomes presented in study M14-032 and the supportive historical evidence from the Mato et al. 2017 study, the unmet need in this population and concerns related to the feasibility of conducting a randomized controlled trial (RCT). These deliberations are summarized below.

pERC re-deliberated on the results of the M14-032 trial and noted that although the medians have not been reached for PFS or OS, the magnitude of PFS and OS rates observed at one year are longer than what are seen with historical outcomes. pERC further noted that the historical data presented within the CGP's clarification in the Clinical Guidance Report and referred to by the stakeholders in their feedback are mostly based on outcomes that employed the use of agents that are not available to patients in Canada (e.g., idelalisib plus rituximab following ibrutinib, re-treatment with chemo-immunotherapy, or early use of venetoclax). Therefore, the magnitude of effect reported with these historical results are likely overestimated for the Canadian context. Based on this, pERC agreed that the improvements in PFS and OS rates at one year observed in the M14-032 trial are meaningful in a setting where no other effective therapeutic options are available and the clinical course is aggressive. pERC, however, re-iterated that there is minimal information on the methodology in the Mato historical data, and therefore the results could be prone to bias and must be interpreted with caution. pERC also considered that the ORR from the M14-032 trial was high in this population and that complete response, although occurring in a small

proportion of patients, is not typically anticipated in this disease setting. pERC therefore agreed that the observed ORR was likely meaningful in this setting.

During the deliberation on the Initial Recommendation, the evidence available to the Committee for deliberations was based on the full M14-32 trial, which included patients previously treated with either ibrutinib and/or idelalisib plus rituximab as their last BCRi. pERC noted that a subgroup analysis from the M14-032 study in patients who have previously received ibrutinib as their last BCRi was published after the posting of the Initial Recommendation. During re-deliberations, pERC acknowledged that this subgroup analysis from the full M14-32 trial was more representative of the Canadian context as ibrutinib is the preferred option since idelalisib plus rituximab has limited use in Canadian jurisdictions. The results of this publication were consistent with the outcomes observed in the overall trial results available to the pCODR reviewers at the outset of the review. The final results for the M14-32 trial are expected at the end of 2018. pERC members agreed that these data would be more valuable when provided early in the course of the review. Notably, the clinical evidence considered during pERC re-deliberations did not include any new evidence.

pERC also reiterated that the M14-032 trial evaluated patient-reported outcomes using a number of questionnaires to measure global health status (GHS), functional status, and symptoms. When evaluated within the individual cohorts of the trial, clinically meaningful improvements were seen in a number of QoL scales. pERC considered the totality of the available QoL data and agreed that there were variable changes in QoL measures, with improvements from baseline and declines from baseline observed. In re-deliberating on the safety profile of venetoclax, pERC further considered feedback from stakeholders indicating that tumour lysis syndrome (TLS) is now better managed in the clinical setting as the ramp-up dosing of venetoclax has minimized these concerns. Monitoring for TLS can also be done in an outpatient setting through intensive clinical and biochemical laboratory monitoring. Overall, pERC agreed that the toxicity profile of venetoclax was manageable. Notably, there may be occasions where patients at high risk will need to be managed in hospital.

pERC discussed the generalizability of the M14-032 trial results. Based on input from the CGP and as discussion in the Mato et al. 2017 study, pERC noted that more patients will likely discontinue treatment with ibrutinib due to intolerance as opposed to disease progression. Although the M14-032 trial did not include patients who were intolerant to their last prior BCRi, pERC agreed that the trial results are generalizable in this patient population, that is, those who are intolerant to ibrutinib. Furthermore, there was some evidence in the Mato et al. historical data to suggest that patients who are intolerant to their last BCRi and are subsequently treated with venetoclax have a larger magnitude of benefit. pERC however acknowledges that this finding is uncertain and it is unclear how large such a difference in the magnitude of benefit might be. Furthermore, there is minimal information on the methodology in the Mato historical data; therefore, the results could be prone to bias and must be interpreted with caution. Additionally, pERC agreed that the M14-032 trial results should not be generalized to patients who have not previously been treated with chemoimmunotherapy (except in patients who have the del17p mutation), patients who are intolerant to front-line ibrutinib (except in patients with the del17p mutation), and patients who have not previously been treated with a BCRi.

pERC also re-deliberated on the unmet need in this population and the feasibility of conducting an RCT. pERC acknowledged the strength of the rationale provided in the feedback from the submitter, patient groups, and registered clinicians, and the response from the CGP. pERC reiterated that patients with CLL who are relapsed or refractory to a BCRi have a poor prognosis and limited treatment options. Therefore there is a need for effective treatment options in a setting where available agents are mostly used with palliative intent. In considering the feasibility of conducting an RCT, pERC noted that there is a large prevalent population which could have been randomized at the outset of the M14-032 study to receive palliative agents considered appropriate at the time or to venetoclax. Based on the feedback received from stakeholders and the CGP, pERC acknowledged that there is no longer equipoise to conduct an RCT, as there is sufficient consensus within the clinical community that venetoclax is superior to palliative treatment. pERC further noted that its role as a Health Technology Assessment (HTA) body is to determine the net clinical benefit and cost-effectiveness of an agent relative to available agents in consideration of other factors, including patient perspectives and clinical evidence. The resulting recommendation is greatly influenced by the robustness of the clinical evidence provided. Having taken these factors into account, pERC reiterated that conclusions that can be drawn from phase II non-comparative data are not as robust as those that can be drawn from RCTs, making it difficult to determine the magnitude of long-term benefit with venetoclax. pERC further noted that phase II trials are

hypothesis-generating and their intent is to determine whether there is sufficient promise to proceed to a phase III confirmatory trial. pERC considers the evidence-generation process as outlined in the hierarchy of clinical trial design a benchmark and expressed concern at the growing number of regulatory and HTA decisions being requested based on phase II non-comparative evidence with limited follow-up data. Following a lengthy discussion on these factors, pERC was swayed by the totality of evidence and feedback received from stakeholders and agreed that there may be a net overall clinical benefit with venetoclax in this population. pERC however stressed that considerable uncertainty remains in the magnitude of benefit with venetoclax. Based on these discussions, pERC agreed that additional clinical and safety data should be made available to the CADTH pCODR reviewers and pERC for a reassessment once the final results are reported for the M14-032 trial or once more robust clinical data are available for venetoclax in this setting.

pERC considered a joint submission from two patient advocacy groups: Lymphoma Canada (LC) and CLL Patient Advocacy Group (CLLPAG)for venetoclax and noted that patients desire a new treatment option that provides disease control and improvements in QoL while offering ease of administration relative to other options. Upon reconsideration of the Initial Recommendation, pERC agreed that there may be a net overall clinical benefit with the use of venetoclax based upon the one-year PFS and OS rates and proportion of patients achieving ORR. Based on feedback from the patient advocacy group, the ability of venetoclax to prolong survival in a large proportion of patients is a meaningful outcome given the poor prognosis of patients and lack of effective treatment options. Having considered this feedback, pERC agreed that venetoclax aligns with patient values. pERC further agreed that venetoclax aligns with patient values as an oral treatment option with a manageable toxicity profile. pERC however acknowledged that there were variable changes in QoL measures, with both improvements and declines from baseline observed.

pERC deliberated upon the cost-effectiveness of venetoclax compared with rituximab monotherapy or rituximab plus HDMP. In the absence of an established standard of care, pERC accepted that rituximab monotherapy or rituximab plus HDMP are reasonable options to use as comparators. Although these are considered to be ineffective treatment options, pERC noted that the clinical effect estimates were largely based on immature PFS and OS data from a non-randomized study and extrapolating beyond the available trial data. Given the uncertainty in these estimates, pERC agreed with the EGP's reanalysis exploring the upper and lower bounds of the confidence interval on the hazard ratio for PFS and OS. pERC noted that OS had the largest impact on the incremental cost-effectiveness ratio. Therefore, due to limitations in the available non-randomized clinical evidence for venetoclax and the absence of long-term data on the potential survival benefit gained in this setting, pERC concluded that it was challenging to determine the true incremental cost-effectiveness ratio. Overall, pERC concluded that, at the submitted price, venetoclax could not be considered cost-effective compared with available therapies. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer regarding the appropriateness of using deterministic analyses to present reanalysis estimates by the EGP. pERC agreed with the EGP's clarification that using the deterministic analysis is not ideal, as stated in the CADTH Guidelines for Economic Evaluations, which specify that probabilistic analysis should be used. In this instance, and given the lack of more robust evidence, pERC agreed with the EGP's attempt to explore the uncertainty in the available data as captured within the lower and upper bounds of the 95% confidence intervals for PFS and OS. The EGP also noted that the available probabilistic analysis did not appear to fully capture this uncertainty in the estimates for PFS and OS. Therefore, presenting a series of scenario analyses around the 95% confidence intervals was the best alternative with the submitted model. Having discussed the EGP's wide range of incremental cost-effectiveness ratios (ICERs) provided through this method, pERC agreed that the ICER is likely close to the middle of this range. pERC acknowledged that an OS and PFS benefit may have been demonstrated; however it is unclear what the magnitude of benefit will be without long-term data. Overall, pERC reiterated that, at the submitted price, venetoclax is not cost-effective. pERC highlighted that additional cost-effectiveness data should be made available to CADTH's pCODR and pERC for a reassessment once the final results are reported for the M14-032 trial or when more robust clinical data become available for venetoclax in this setting. Until such data are made available, jurisdictions should consider a time-limited reimbursement of venetoclax. pERC noted that this strategy would help ensure the equitable and timely access of promising treatments to patients while ensuring that treatment option considered for public reimbursement adhere to a level of rigour that sufficiently demonstrates effectiveness.

pERC considered the feasibility of implementing a reimbursement recommendation for venetoclax. pERC noted that the prevalent population of patients with CLL who are relapsed or refractory to a BCRi is large and that the anticipated budget impact of venetoclax is substantial. Furthermore, with the inclusion of

patients who are intolerant to prior ibrutinib into the reimbursement population, pERC concluded that the budget impact of venetoclax will be even larger than anticipated. This population of patients intolerant to ibrutinib or a BCRi were not accounted for in the submitted BIA. pERC noted that the BIA is sensitive to the market share of venetoclax and discontinuation rates of venetoclax. pERC therefore agreed that a substantial price reduction is required to reduce the potential budget impact of venetoclax.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from stakeholders clarifying that concerns related to TLS are manageable. pERC noted that the ramp-up dosing of venetoclax has greatly reduced the risk of TLS and it is no longer anticipated that all patients would need to be admitted to hospital for treatment. Feedback from registered clinicians and the CGP indicated that intensive clinical and biochemical laboratory monitoring in an outpatient setting would be sufficient to monitor these patients.

EVIDENCE IN BRIEF

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

- 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 (BIA)
- guidance from the pCODR clinical and economic review panels
- joint input from two advocacy groups: Lymphoma Canada and CLL Patient Advocacy Group
- input from registered clinicians
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group (CLL Patient Advocacy Group)
- registered clinicians (Cancer Care Ontario Hem DAC and individual clinicians)
- the PAG
- the submitter (AbbVie Corporation)

The pERC Initial Recommendation was to not recommend reimbursement of venetoclax for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-cell receptor inhibitor (BCRi). Feedback on the pERC Initial Recommendation indicated that the PAG agreed with the Initial Recommendation and the manufacturer, patient advocacy group, and registered clinicians disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of venetoclax (Venclexta) as monotherapy for the treatment of patients CLL who have received at least one prior therapy and who have failed a BCRi.

Studies included: Non-randomized trial, parallel arms, and interim results

The pCODR systematic review included one non-randomized, non-comparative, open-label, phase II trial (M14-032), which evaluated the use of venetoclax in patients who have previously received treatment with ibrutinib and/or idelalisib and who have relapsed on treatment or have experienced progression after discontinuation of either of these agents. Although the study was multi-centre, no Canadian sites were included. Key inclusion criteria required that patients must have had relapsed or refractory disease with an indication for treatment. Refractory disease or recurrence must have occurred after treatment with either one of the B-cell receptor signalling pathway inhibitors ibrutinib or idelalisib and met one of the following criteria: (1) treatment failure with either of these agents or (2) progression during treatment or after discontinuation or either of these agents. During pERC's deliberation on the Initial Recommendation, the M14-032 trial data were based on an interim analysis of data that had not been peer-reviewed or published.

pERC noted that the results of the subgroup analysis of patients in the M14-032 trial who received ibrutinib as their last BCRi have been published since the posting of the Initial Recommendation. pERC acknowledged that this population was more representative of the Canadian context as ibrutinib is the preferred option and idelalisib plus rituximab has limited use in Canadian jurisdictions. The final results for the M14-32 trial are expected at the end of 2018. pERC members agreed that these data would be more valuable when provided early in the course of the review.

The pCODR review also provided contextual information on two retrospective studies. Mato et al. 2016 (n = 178) investigated reasons for BCRi discontinuation, outcomes after stopping therapy, and the impact that BCRi sequencing had on outcomes. Mato et al. 2017 (n = 683) investigated rates and causes of discontinuation to assess outcomes following discontinuation and to define the best sequencing strategy utilizing kinase inhibitors and venetoclax. Data were gathered through chart reviews for both studies, and Mato et al. 2017 also utilized institutional clinical or pathological databases and electronic medical records. Both studies reported that among patients treated with an alternate BCRi (after an initial BCRi),

those who were intolerant to the initial BCRi had a superior PFS as compared with those for whom disease progression was the reason for discontinuation. Mato et al. 2017 concluded that ibrutinib appears superior to idelalisib as the first BCRi and, in the setting of BCRi failure, alternate BCRis or venetoclax appear superior to chemoimmunotherapy combinations. Further, the use of venetoclax might be superior to idelalisib upon ibrutinib failure. pERC acknowledged that retrospective analyses are prone to reporting bias, information bias, selection bias, etc. Therefore these results, though promising, must be interpreted with caution. Upon reconsideration of the pERC Initial Recommendation, pERC noted feedback from stakeholders regarding the results from the Mato et al. publications. pERC noted that patients in this historical data received agents that are not available to patients in Canada (e.g., idelalisib plus rituximab following ibrutinib or re-treatment with chemo-immunotherapy). Therefore, the magnitude of effect for comparators reported with these historical results are likely overestimated for the Canadian context. Notably, despite this, venetoclax appears to be superior to these unavailable agents. pERC agreed that the benefit observed with the use of venetoclax in this historical data supports results observed in the M14-032 trial and is therefore, meaningful. Furthermore, pERC noted that this evidence has not been confirmed by results from comparative clinical trials and reiterated that there is minimal information on the methodology in the Mato publications. Therefore the results could be prone to bias and must be interpreted with caution.

Patient populations: Relapsed or refractory CLL after treatment with ibrutinib and/or idelalisib

A total of 127 patients were enrolled in the M14-032 trial: 43 into arm A (patients with relapsed or refractory CLL after ibrutinib treatment), 21 into arm B (patients with relapsed or refractory CLL after idelalisib treatment), and 63 into the expansion cohort (patients previously treated with either ibrutinib (n = 53) or idelalisib (n = 22). A total of 22 out of 127 patients (17.3%) received both ibrutinib and idelalisib as a prior line of therapy. Most patients had Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (32.3%) or 1 (59.1%). Patients were classified into three risk categories based on their tumour burden prior to venetoclax administration, and 35 out of 127 patients (28%) were at high risk for tumour lysis syndrome (TLS). A total of 57 patients (44.9%) harboured the chromosome 17p13.1 deletion (del(17p)) and/or TP53 mutation or both as assessed by the investigator's local laboratory. Most patients were male (70.1%) and white (92.1%), and 58.3% were at or above the age of 65. The December 2017 Lancet Oncology publication of the M14-032 trial was based on an unplanned June 2017 data cut and reported on 91 patients (43 from the main cohort and 48 from the expansion cohort) who were previously treated with ibrutinib. Notably, in the overall trial there were 96 patients who were previously treated with ibrutinib but the publication reported on 91. It is unclear why five patients were excluded from the analysis and what the impact of these missing patients would have on the results in this subgroup analysis. Baseline characteristics in the subgroup analysis were similar to those reported for the overall trial.

All patients received single daily oral doses of venetoclax, starting with 20 mg and increasing weekly to a target dose of 400 mg over four to five weeks. Patients were able to continue receiving venetoclax for up to two years provided they continued to tolerate the drug, had no evidence of disease progression, and did not meet any of the criteria for discontinuation. The anticipated median duration of treatment was approximately one year.

To further reduce the risk of TLS, patients received prophylaxis with uric acid–lowering agents starting at least 72 hours prior to the first venetoclax dose, and patients with high tumour burden were hospitalized. Patients also received oral hydration irrespective of TLS risk category starting at least 48 hours prior to each dose. Patients unable to maintain adequate oral hydration or those with medium or high risk for TLS were also given intravenous hydration. Patients were monitored for TLS at the first dose and at dose increases, and any changes that identified increased risk were immediately addressed.

Key efficacy results: Meaningful improvement in progression-free survival and overall survival rate at one year

The key efficacy outcome deliberated on by pERC was objective response rate (ORR). No formal a priori statistical hypothesis plan was conducted on the primary end point of ORR. However, a sample size of 60 patients ensured that the distance of the true rate would be within 14% of the observed rate with 95% confidence.

Investigator-assessed ORR was 56.7% (n = 72) in all patients (95% confidence interval, 47.6 to 65.5). Among these, 8.7% (n = 11) were complete response and 48% (n = 61) were partial response. In the

subgroup of patients with 17p deletion and/or p53 mutation or both, ORR was reported in 66.7%, 80.0%, and 50.0% in arm A, arm B, and the expansion cohort, respectively. Secondary outcomes deliberated by pERC included progression-free survival (PFS) and overall survival (OS). Medians were not reached for either outcome by the January 31, 2017, cut-off date. Kaplan–Meier estimates demonstrated that, at 12 months, 74.2% of patients had not progressed. As of the January cut-off date, 14 deaths had occurred (out of 127 patients). Kaplan-Meir estimates reported that, at 12 months, OS rates were 88.2%, 95.2%, and 96.2% in arm A, arm B, and the expansion cohort, respectively. pERC noted input from CGP indicating that at least a one-year to two-year OS benefit would be anticipated with the use of venetoclax in this setting. Based on the June 2017 data cut (Lancet Oncology publication) reported for 91 patients previously treated with ibrutinib, investigator-assessed ORR was 64.8% (95% confidence interval, 53% to 74%). Rates of complete response (8.8%) were similar to what were seen in the overall trial results. For secondary outcomes, the estimated PFS and OS rates were 75% and 91% at one year, respectively.

During the deliberation on the Initial Recommendation, the Committee noted considerable uncertainty in the available data due to the absence of mature PFS and OS data, the interim nature of the available data, the short trial follow-up, and low rates of complete responses to treatment. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the submitter, registered clinicians, and a patient advocacy group and received clarification from the pCODR Clinical Guidance Panel (CGP) on the interpretation of the available evidence. pERC had substantive re-deliberations on the results of the M14-032 trial and noted that although medians have not been reached for PFS or OS, the magnitude of PFS and OS rates observed at one year are longer than what is seen with historical outcomes. pERC also agreed that longer term follow-up data may confirm whether a survival advantage up to two years will be demonstrated with the use of venetoclax. pERC also had more substantive discussion on the Mato publications and noted that the historical data are mostly based on outcomes that employed the use of agents that are not available to patients in Canada (e.g., idelalisib plus rituximab following ibrutinib). Therefore, the magnitude of effect reported with these historical results are likely overestimated for the Canadian context. Based on this, pERC agreed that the improvements in PFS and OS rates at one year observed in the M14-032 trial are meaningful, particularly in the context of a disease with a poor prognosis and absence of alternative effective treatment options. pERC also considered that ORR from the M14-032 trial was high in this population and that complete remission, although occurring in a small proportion of patients, is not typically anticipated in this disease setting. pERC therefore agreed that the observed results in the M14-032 trial demonstrate meaningful outcomes for patients. pERC however reiterated that given the sort duration of follow-up and phase II design of the study, there is uncertainty in the magnitude of long-term benefit with venetoclax. Based on these discussions, pERC agreed that additional clinical and safety data should be made available to the CADTH pCODR reviewers and pERC for a reassessment once the final results are reported for the M14-032 trial or more robust clinical data are available for venetoclax in this setting.

Patient-reported outcomes: Clinically meaningful improvement and worsening from baseline

Patient-reported outcomes were evaluated in the M14-032 study using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30), the EORTC QLQ for CLL 16 (QLQ-CLL16) and the EuroQol Visual Analogue Scale. Patient-reported outcomes as an exploratory outcome in the M14-032 trial.

In arm A, minimally important improvements were measured at all time points for global health status, role functioning, and social functioning. Financial difficulties had clinically meaningful improvement at some measurement time points. Clinically meaningful worsening was measured for diarrhea. In arm B, clinically meaningful worsening of diarrhea, pain, and cognitive functioning was reported between baseline and the final observation. In cohort B, some of the measured quality-of-life (QoL) scales demonstrated changes greater than 5 points (both minimally important improvement and decline) at different measurement time points. Based on aggregate data for all three cohorts, both the EORTC QLQ-CLL16 and the EORTC QLQ-C30 scales demonstrated clinically important improvement of fatigue. Moderate to large changes from baseline scores were also reported for social problems, with minimal clinically important worsening being reported at all time points. pERC discussed the QoL data available and agreed that there is indication of both improvement and worsening on a number of scales both in the aggregate data and in individual cohorts.

Safety: Manageable toxicity

pERC discussed the safety profile of venetoclax and noted it to be manageable. Grade 3 or 4 adverse events were reported in 93.0% of patients in arm A, 81.0% of patients in arm B, and 71.4% of patients in the expansion cohort. The three most common grade 3 or 4 adverse events by study arm were as follows:

- arm A: anemia (32.6%), decreased neutrophil count, and neutropenia (27.9% each)
- arm B: neutropenia (42.9%), thrombocytopenia (23.8%), and anemia (14.3%)
- expansion cohort: neutropenia (33.3%), anemia (23.8%), and decreased neutrophil count (17.5%).

Notably, most of these were disease-related symptoms that patient input had outlined as being most important to control with new treatments. Treatment-emergent serious adverse events were reported in 46.5% of all patients.

pERC noted that TLS is an adverse event that required monitoring in this population during treatment. There were no cases of clinical TLS reported in the trial. Upon reconsideration of the Initial Recommendation, pERC noted feedback from stakeholders on the safety profile of venetoclax as related to the risk of TLS and associated management strategies. This feedback from stakeholders and further clarification from the CGP indicated that TLS is now better managed in the clinical setting, as the ramp-up dosing of venetoclax has minimized these concerns. pERC also noted feedback indicating that the intensive clinical and biochemical laboratory monitoring in an outpatient setting may be sufficient to monitor for TLS. Based on this feedback, pERC therefore agreed that the risk of TLS is now reduced and better managed. As of the January 31, 2017, cut-off date, 14 patients had died. Seven patients died within 30 days of the last dose of venetoclax and experienced fatal adverse events, and seven deaths were reported during survival follow-up. Among the seven deaths that occurred within 30 days of treatment, causes included septic shock, death not otherwise specified, multiple organ dysfunction syndrome, asphyxia, malignant neoplasm attributed to disease progression, *corynebacterium* sepsis (not related to venetoclax), and cytokine release syndrome (also not related to disease progression based on the investigator's assessment).

Need and burden of illness: Need in patients with and without the del(17p) mutation

CLL is a common leukemia with a long natural history. Each year, approximately 2,400 Canadians are diagnosed with CLL and 650 die from it, with a median age at diagnosis of 72 years. The most important prognostic markers currently in clinical practice are those that detect a defective TP53 gene (either by interphase FISH [fluorescence in situ hybridization] cytogenetics as del(17p) or by sequencing to assess for gene mutations); a functioning p53 is an essential cofactor for programmed cell death, and patients with this abnormality are generally resistant to chemotherapy and radiotherapy. In patients without the del(17p) mutation, front-line treatment typically involves fludarabine/cyclophosphamide/rituximab in fit patients and chemoimmunotherapy in frail patients. This is followed by ibrutinib in the relapsed or refractory setting. The outlook of patients following relapse is poor as there are no effective treatment options. For the subgroups of patients who have CLL and high-risk disease (i.e., del(17p)) prognosis is especially poor, as the presence of these mutations is associated with resistance to standard chemoimmunotherapy, and front-line treatment would employ ibrutinib or idelalisib plus rituximab. There is currently no consensus on treatment options for patients who have previously received treatment with ibrutinib and/or idelalisib and who have relapsed on treatment or have experienced progression after discontinuation of either of these agents. Available agents for use may include single-agent rituximab or rituximab plus high-dose methylprednisolone (HDMP). In these patients with relapsed or refractory disease, the median overall response rates are poor (20% to 50%), and PFS has typically been less than six months. Therefore, more effective agents with activity in this biologically aggressive subgroup are needed. In previously untreated patients, the incidence of TP53 gene abnormalities is approximately 10% to 12%. In the relapsed or refractory setting, through the process of clonal evolution, the incidence of TP53 abnormalities can increase up to approximately 30%. Patients with the del(17p) mutation typically receive ibrutinib in the front-line setting. For patients who develop resistance or intolerance to available tyrosine kinase inhibitors (TKIs), there is currently no effective alternative therapy and prognosis is very poor. Therefore, pERC agreed that there is a need for additional effective therapies in this patient population, particularly in patients with the del(17p) mutation. Upon reconsideration of the Initial Recommendation, pERC reiterated that patients with CLL who are relapsed or refractory to a BCRi have a poor prognosis and limited treatment options. Therefore, there is a need for effective treatment options in a setting where available agents are mostly for palliative intent.

Registered clinician input: High response rates with venetoclax

According to registered clinician input, patients in whom TKIs fail have a very short life expectancy (approximately three months based on prior studies) and no other viable treatment options. Clinician input indicates that venetoclax is the only agent with documented efficacy in this population. Registered clinician input indicated that the key benefits of venetoclax were its high response rates and durable responses in a patient population with no other effective treatment options. Response rates with venetoclax were also indicated to be considerably higher when compared with treatment with alternate TKI after failure of a first TKI. During the deliberation on the Initial Recommendation pERC acknowledged that the evidence (M14-032 trial) suggests that there is promising antitumour activity with venetoclax; however, the magnitude of effect was uncertain given the lack of comparative data on long-term outcomes important to patients, such OS and PFS. Upon reconsideration of the pERC Initial Recommendation, pERC considered the clarification from registered clinicians and feedback from registered clinicians, two patient advocacy group and the manufacturer on the interpretation of the available evidence. Based on this feedback and substantive deliberation, pERC agreed that in a setting where there is poor prognosis and no effective treatment options, the magnitude of PFS and OS rates observed at one year are meaningful. These results were also longer than what is seen with historical outcomes. pERC also agreed that ORR from the M14-032 trial was high in this population and that complete remission, although occurring in a small proportion of patients, is not typically anticipated in this disease setting. pERC therefore agreed that the observed results in the M14-032 trial demonstrate meaningful outcomes for patients.

Clinician input identified the possibility of discontinuing treatment following deep molecular remission. pERC noted input from the CGP indicating that deep molecular remission is assessed through minimal residual disease. Given that minimal residual disease was an exploratory end point, it is difficult to determine if patients have truly achieved benefit from it. Therefore conclusions on treatment discontinuation cannot be made based on this criterion. As an oral therapy, venetoclax is also a convenient option.

PATIENT-BASED VALUES

Values of patients with chronic lymphocytic leukemia: Symptom control and quality-of-life impact

pERC deliberated upon patient advocacy group input for venetoclax and discussed the values of patients with previously treated CLL.

Patient input indicated the top three CLL symptoms that affected QoL at diagnosis and on an ongoing basis were fatigue/lack of energy, increasing lymphocyte count, and enlarged lymph nodes. Psychological aspects of CLL (and small lymphocytic lymphoma) affecting patients and caregivers the most included stress of diagnosis, anxiety/worry, difficulty sleeping, and depression. Some patients also \ experienced difficulties with concentration, emotions, and mood swings. Infections, thrombocytopenia, neutropenia, viral infections, anemia, fatigue/lack of energy, white blood cell count decrease, fever, lymph node size, and enlarged spleen or abdominal discomfort were rated as being important symptoms to control by 60% or more of patients providing input.

Among 179 individuals providing input, most indicated that their current treatments are unable to manage their symptoms. Patients indicated that the most difficult to tolerate side effects were fatigue, nausea, and frequency of infections. Some patients indicated that they were unable to access treatment in their own communities. Caregivers providing input indicated that their ability to travel, spend time with family or friends, concentrate, and fulfill family obligations are impacted significantly as a result of caring for a patient with CLL.

pERC considered that symptom control and QoL improvement were important outcomes for patients. Based on the results of the M14-032 trial, there appear to be improvements and worsening of QoL in a number of scales but the toxicity profile of treatment was deemed to be manageable.

Patient values on treatment: Treatment options, oral administration, targeted therapy, increased effectiveness

Among 301 patients providing input, nearly all (n = 286) indicated the importance of having choice in therapy. A large number of patients (133 out of 301) indicated that they would be willing to take a drug with potentially serious side effects if it was recommended to be the best option for them by their doctor. When asked to prioritize the important aspects of a new therapy, 72 out of 162 patients prioritized increased effectiveness, 40 rated decreased toxicities as most important, 12 rated remissions as most important, 12 wanted accessible and affordable treatments, 11 wanted an improved QoL, and nine stressed the importance of an oral therapy. Patients want to transition from an era of chemotherapy to an era of targeted therapy with proven efficacy in treating a range of patients, including those with poor prognostic factors and those with advanced age and existing comorbidities. Patients seek individualized choice in treatment that will offer disease control and improve QoL while offering ease of use relative to other available treatments.

Twenty-one patients had direct experience with venetoclax, among whom four were from Canada. Only eight out of 21 patients had previously been treated with ibrutinib and/or idelalisib and experienced resistance, failure, or intolerance. Side effects of venetoclax were rated to be mild and quickly dissipating or effectively treated with medication. Side effects reported by participants included diarrhea (n = 8), neutropenia (n = 7), fatigue (n = 6), nausea (n = 5), thrombocytopenia (n = 2), upper respiratory tract infection (n = 1), and TLS (n = 1).

During the deliberation on the Initial Recommendation, pERC noted that uncertainty in the net clinical benefit of venetoclax tempered its conclusion on alignment with patients' values. At the time the Committee had agreed that venetoclax aligned with patient values of having an additional treatment option, control of disease symptoms, and an oral route of administration; however, in the absence of conclusive data on the clinical effectiveness of venetoclax, the Committee concluded, at the time, that venetoclax only partially aligned with patient values. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the patient advocacy groups on the interpretation of the available evidence as related to patient values. pERC reiterated that there is a need for effective options in this setting, as the prognosis for patients is poor. pERC further acknowledged that patients desire access to effective therapies in a timely manner and discussed the Committee's mandate to ensure that therapies recommended for reimbursement adhere to a level of rigour that has sufficiently demonstrated effectiveness. In this instance, pERC agreed there is no longer equipoise to conduct a randomized trial in this setting, as there is sufficient consensus within the clinical community that venetoclax is the most effective agent. Based on these discussions, the Committee agreed that the magnitude of PFS and OS rates observed at one year and the ORR rate are meaningful to patients, as they demonstrate activity in a setting where there are no effective treatment options. Overall, despite the uncertainties that still remain in the long-term benefit anticipated with this therapy, pERC agreed that venetoclax aligns with patient values.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis and cost-effectiveness analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis and a cost-effectiveness analysis of venetoclax compared with rituximab monotherapy or rituximab plus HDMP in patients with CLL who have received at least one prior therapy and who have failed a BCRi.

Basis of the economic model: Uncertain clinical inputs

Costs considered in the economic model included drug costs, costs to manage adverse events, TLS prophylaxis, and routine care and monitoring costs. The key clinical outcomes considered in the model were PFS, OS, and utilities.

Given the absence of robust direct evidence, the clinical effect considered in the analysis was based on data for the comparator arm from published survival curves from NICE (National Institute for Health and Care Excellence) submissions for idelalisib in the relapsed or refractory CLL setting. pERC acknowledged considerable limitations in the results of this analysis and agreed that caution should be used in interpreting the results.

Drug costs: Treatment until progression or maximum two years

Venetoclax costs $6.80 per 10 mg, $33.99 per 50 mg, and $67.99 per 100 mg. The recommended ramp-up dosage for venetoclax includes 2 × 10 mg daily on week one, 1 × 50 mg daily on week two, 1 × 100 mg daily on week three, and 2 × 100 mg daily on week four. All subsequent dosages are 4 × 100 mg daily. At the recommended ramp-up and subsequent dosages, venetoclax costs $62.89 per day and $1,760.88 per 28-day course for the first cycle for the ramp-up stage and $271.95 per day and $7,614.60 per 28-day course for subsequent cycles.

Rituximab costs $4.71 per mg. When used as combination therapy and at the recommended dosage of 375 mg/m^2 on day 1 of cycle 1, 500 mg/m^2 on day 1 and day 5 of cycle 2 and cycle 3, and then 500 mg/m^2 on day 1 of cycles 3 to 6, every 21 days, rituximab costs $190.45 per day and $5,332.54 per 28-day cycle. When used as a single agent and at the recommended dosage of 375 mg/m^2 on day 1 of cycle 1, 500 mg/m^2 on day 1 of cycles 2 to 7, every 28 days for six cycles, rituximab costs $142.84 per day and $3,999.40 per 28-day cycle.

HDMP costs 0.0722 per mg. At the recommended dose of 1 g/m^2 daily for five consecutive days every 21 days for six cycles, HDMP costs $5.85 per day and $163.65 per 28-day course.

Clinical effect estimates: Uncertainty in PFS and OS estimates

pERC deliberated on the cost-effectiveness of venetoclax compared with rituximab or rituximab plus HDMP. In the absence of an established standard of care, pERC agreed that rituximab monotherapy or rituximab plus HDMP are reasonable options to use as comparators. Although these are considered to be ineffective treatment options, the Committee expressed uncertainty in the estimates for long-term benefit with venetoclax given the immaturity of the trial results and lack of direct comparative trials. pERC noted that the clinical effect estimates were largely based on immature PFS and OS data and extrapolating beyond the available trial data. Given the uncertainty in these estimates, pERC agreed with EGP's reanalysis exploring the upper and lower bounds of the confidence interval on the hazard ratio for PFS and OS. pERC noted that OS had the largest impact on the incremental cost-effectiveness ratio. pERC considered input from CGP indicating that a one-year to two-year OS benefit is anticipated with venetoclax and agreed that this is based on clinical opinion. Therefore, due to limitations in the available non-randomized clinical evidence for venetoclax and the absence of long-term data on the potential survival benefit gained in this setting, pERC concluded that it was challenging to determine the true incremental cost-effectiveness ratio. Based on EGP's reanalysis estimates, pERC agreed that venetoclax could not be considered cost-effective compared with available therapies. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer regarding the appropriateness of using deterministic analysis to present reanalysis estimates by the EGP. pERC agreed with the EGP's clarification that using the deterministic analysis is not ideal, as the CADTH Guidelines for Economic Evaluations specify the use of probabilistic analysis. In this instance and given the lack of more robust evidence, pERC agreed with the EGP's attempt to explore the uncertainty in the available data as captured within the lower and upper bounds of the 95% confidence intervals for PFS and OS. The EGP also noted that the available probabilistic analysis did not appear to fully capture this uncertainty in the estimates for PFS and OS. Therefore, presenting a series of scenario analyses around the 95% confidence intervals was the best alternative with the submitted model. Having discussed the EGP's wide range of incremental cost-effectiveness ratios (ICERs) provided through this method, pERC agreed that the ICER is likely close to the middle of this range. pERC acknowledged that an OS and PFS benefit may have been demonstrated; however, it is unclear what the magnitude of benefit will be without long-term data. Overall, pERC reiterated that, at the submitted price, venetoclax is not cost-effective. pERC highlighted that additional cost-effectiveness data should be made available to the CADTH pCODR reviewers and pERC for a reassessment once the final results are reported for the M14-032 trial or once more robust clinical data are available for venetoclax in this setting. Until such data are made available, jurisdictions should consider a time-limited reimbursement of venetoclax. pERC noted that this approach would help ensure equitable and timely access to promising treatments for patients while ensuring that treatment options considered for public reimbursement adhere to a level of rigour that sufficiently demonstrates effectiveness.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Potentially substantial budget impact

pERC considered the feasibility of implementing a reimbursement recommendation for venetoclax. pERC noted that concerns remain regarding TLS with the use of venetoclax, and therefore intensive monitoring and prophylactic measures would need to be taken to prevent TLS in patients. As noted by the Provincial Advisory Group input, this would require additional health care resources to monitor. pERC also noted that the packaging of the venetoclax ramp-up dose requires monitoring to ensure that patients are taking the correct dose on the right day. Upon reconsideration of the Initial Recommendation, pERC considered feedback from stakeholders clarifying that concerns related to TLS are minimal. pERC noted that the ramp-up dosing of venetoclax has greatly reduced the risk of TLS and it is no longer anticipated that all patients would need to be admitted to hospital for treatment. Feedback from registered clinicians and the CGP indicated that intensive monitoring of blood counts and blood chemistry in an outpatient setting would be sufficient.

pERC agreed that venetoclax' oral route of administration creates ease of administration for patients and is an enabler to implementation, pERC considered factors affecting the budget impact and noted that the front-line CLL population is large. pERC therefore agreed that the potential budget impact of venetoclax is uncertain but likely to be high. Furthermore, pERC noted that the drug's high cost is a barrier to implementation. Upon reconsideration of the Initial Recommendation, pERC noted that the prevalent population of patients with CLL who are relapsed or refractory to a BCRi is large and the anticipated budget impact of venetoclax is large. Furthermore, with the inclusion of patients who are intolerant to prior ibrutinib into the reimbursement population, pERC concluded that the budget impact of venetoclax will be even larger than anticipated. This population of patients intolerant to ibrutinib or a BCRi was not accounted for in the submitted BIA. pERC noted that the BIA is sensitive to the market share of venetoclax and discontinuation rates of venetoclax. pERC agreed that a substantial price reduction is required to reduce the potential budget impact of venetoclax.

DRUG AND CONDITION INFORMATION

Drug Information	• Selective inhibitor of B-cell lymphoma 2 (bcl-2) gene • 10 mg, 50 mg, and 100 mg tablet sizes • Recommended dosage of 20 mg daily (week 1), 50 mg daily (week 2), 100 mg daily (week 3), 200 mg daily (week 4), and 400 mg daily for all subsequent doses
Cancer Treated	• Relapsed or refractory chronic lymphocytic leukemia (CLL) previously treated with a B-cell receptor inhibitor (BCRi)
Burden of Illness	• CLL is the most common leukemia in Western countries • Approximately 2,400 Canadians are diagnosed with CLL each year and 650 die from it
Current Standard Treatment	• No standard treatment option • Single-agent chemotherapies (i.e., rituximab)
Limitations of Current Therapy	• No effective treatment options in patients who have failed prior treatment with ibrutinib or idelalisib plus rituximab

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)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Mike Doyle, Health Economist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Lauren Flay Charbonneau and Dr. Craig Earle, who were not present for the meeting
- Dr. Matthew Cheung, who was excluded from voting due to a conflict of interest.
- Cameron Lane, who did not vote due to his role as a patient member alternate.

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Drs. Matthew Cheung, Anil Abraham Joy, and Craig Earle, who were not present.
- Lauren Flay Charbonneau, who was excluded from voting due to a conflict of interest.
- Mike Doyle, who was no longer part of the pERC Committee.
- Cameron Lane, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the 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 pCODR website, and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of venetoclax (Venclexta) for chronic lymphocytic leukemia, through their declarations, seven members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, one 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 pCODR 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 pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

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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