pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
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 pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Venetoclax (Venclexta)

Submitted Funding Request:
For the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and have a 17p deletion

Submitted by:
AbbVie Corporation

Manufactured by:

AbbVie Corporation

NOC Date:
September 30, 2016

Submission Date:
July 8, 2016

Initial Recommendation Issued:
December 1, 2016

pERC RECOMMENDATION	pERC does not recommend reimbursement of venetoclax for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (CLL) with 17p deletion who have received at least one prior systemic regimen. The Committee made this recommendation because it was unable to conclude that, based on the available evidence, there is a net clinical benefit of venetoclax compared with appropriate comparators. While pERC noted that there is a need for additional effective treatments in this setting and that venetoclax produces anti-tumour activity, the Committee concluded that there was considerable uncertainty in the magnitude of extra clinical benefit of venetoclax compared with appropriate comparators with regard to outcomes important to decision-making, such as overall survival (OS), progression-free survival (PFS), and quality of life. pERC concluded that venetoclax partially aligned with patient values because of the drug's ability to control disease symptoms and bring about improvements in quality of life, despite the lack of comparative evidence. Given the considerable uncertainty in the estimates for efficacy, the Committee was unable to draw a conclusion on the cost-effectiveness of venetoclax compared with ibrutinib. pERC also highlighted that the potential budget impact of venetoclax is likely underestimated and could be substantial.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified

SUMMARY OF pERC DELIBERATIONS

CLL is a common leukemia with a long natural history. Each year, approximately 2,400 Canadians are diagnosed and 650 die from CLL, 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 cytogenetics as del17p, or sequencing to assess for gene mutations); a functioning p53 is an essential cofactor for programmed cell death and patients with this high-risk disease (i.e., chromosome 17p13.1 deletion: del(17p)), have an especially poor prognosis. More effective agents with activity in this biologically aggressive subgroup are needed. The incidence of this mutation among CLL patients is 10% to 20% in untreated patients and increases, through clonal evolution, to 30% in the relapsed or refractory setting. New therapies have recently become available for the treatment of newly diagnosed or relapsed or refractory patients with CLL with the del(17p). The current standard of treatment for patients who have CLL with the del(17p) and who have received at least one prior systemic regimen is ibrutinib or idelalisib plus rituximab. For patients who develop resistance or intolerance to available tyrosine kinase inhibitors, there is currently no effective alternative therapy and prognosis is very poor. pERC, therefore, agreed that there is a need for effective treatment options in this patient population.

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 open-label, non-randomized trial, M13-892, which evaluated the use of venetoclax in patients with relapsed or refractory CLL harbouring the del(17p). The Committee was not satisfied that the available evidence clearly demonstrated a net overall clinical benefit of treatment with venetoclax. pERC noted the availability of ibrutinib or idelalisib plus rituximab which are—standard treatment options in this setting — and the absence of robust direct or indirect clinical evidence to assist with making a conclusion on the clinical benefit of venetoclax compared with these standard options. pERC acknowledged that the current evidence shows that there is anti-tumour activity with venetoclax; however, the magnitude of effect compared with available effective therapies is uncertain, given the lack of comparative data and long-term data on outcomes important to patients, such as OS and PFS. pERC noted that the M13-982 trial evaluated patient-reported outcomes using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and the EORTC Quality of Life Questionnaire–Chronic Lymphocytic Leukemia 16 (QLQ-CLL16). Although minimally important differences (i.e., clinically relevant differences) were attained in the global QLQ-C30 scale and in a number of subscales of both instruments, pERC agreed that in a treatment setting in which patients would receive treatment until disease progression or unacceptable toxicity, an outcome based on a change from baseline until week 24 may not capture the full impact of venetoclax on patients' quality of life throughout treatment. Given that there are effective treatment options in this setting, pERC also considered that there are no data to determine the comparative impact of venetoclax on patients' quality of life. pERC discussed the safety profile of venetoclax and noted it to be generally well tolerated, with manageable toxicities. Based on the mechanism of action of venetoclax, a concern remains regarding tumour lysis syndrome (TLS), which occurred in 5% of patients in the trial. pERC agreed that appropriate risk assessment (low, medium, and high risk for TLS), preventive measures, and intensive monitoring would be required for the management of TLS in patients receiving venetoclax as was done in the trial. This may include periodically hospitalizing patients during the first month of treatment to appropriately manage potential toxicities during the ramp-up phase of treatment. Therefore patients would need to be within close proximity of a hospital for the first month of therapy. pERC noted input from the pCODR Clinical Guidance Panel (CGP), indicating that a randomized controlled trial is unlikely to be conducted in this setting because of the small patient population. In considering the number of patients recruited in the M13-982 trial and other trials that have randomized similar numbers of patients with the del(17p) as subgroups in broader studies, the Committee felt that a sufficient number of patients with the del(17p) likely existed to conduct a randomized controlled trial trial.

pERC discussed the available evidence from the M13-982 trial and the ongoing M14-032 trial as related to patients with relapsed or refractory CLL harbouring the del(17p) and who have previously failed treatment with ibrutinib or idelalisib plus rituximab. pERC considered the evidence in this population to

be preliminary as the ongoing M14-032 trial has reported only interim results, in abstract form, for a total of 23 patients, while the M13-892 trial included a total of five patients in this setting. In deliberating on the evidence for this patient population, pERC recognized the significant need for treatment options in this setting, as the prognosis of patients resistant or intolerant to available tyrosine kinase inhibitors is very poor and these patients would have no reasonable treatment options remaining. However, in the absence of robust peer-reviewed evidence confirming the current preliminary results, the Committee could not confidently make conclusions from a non-randomized ongoing trial with only an interim analysis reported.

The Committee had a lengthy and robust discussion on the evidence presented for venetoclax and various opinions were expressed. The Committee agreed that, in patients with del(17p) who have previously been treated with ibrutinib or idelalisib plus rituximab, there is a significant unmet need for effective treatments. However, given the considerable uncertainty regarding the available preliminary evidence from study M14-032, pERC was unable to come to a conclusion on the comparative efficacy and safety in this population. Furthermore, for the broader population of patients with del(17p) who have received at least one prior therapy, pERC acknowledged that it has accepted evidence from non-comparative studies in previous submissions of other therapeutics for reasons that are context (drug and disease) specific. However, in this instance, given the availability of effective treatment options (i.e. ibrutinib, idelalisib plus rituximab), the absence of a clear advantage over these effective treatment options and the short trial follow-up period (lack of mature results for PFS and OS — outcomes important for decision-making), the Committee was unable to draw a conclusion on the magnitude and direction of benefit with venetoclax in this patient population.

pERC deliberated upon the alignment of venetoclax with patient values based on submissions from two patient groups and on the results of the M13-982 trial. In alignment with the patient value of having oral treatment options, pERC noted that venetoclax provides another oral option with a manageable toxicity profile. The Committee, however, noted that TLS was reported in five patients in the M13-982 trial. As part of the trial design, TLS was managed through risk assessment and stringent measures for prophylaxis and none of the patients who experienced TLS discontinued treatment. pERC however acknowledged that there may be a need to periodically hospitalize patients for TLS prophylaxis during the first month of treatment to appropriately manage potential toxicities during the ramp-up phase of treatment. Therefore patients would need to be within close proximity of a hospital for the first month of therapy. Furthermore, pERC noted patient input which indicated TLS was an adverse event that 40% of patients providing input were unwilling to have as a side effect of treatment. pERC also noted that patients valued treatments that prolonged survival and managed disease and treatment related adverse events. The Committee discussed the lack of comparative evidence on the efficacy and safety of venetoclax against currently available standard treatment options, as well as the absence of long-term follow-up data to understand the impact of venetoclax on these important patient outcomes. Overall, pERC concluded that venetoclax only partially aligned with patient values.

pERC deliberated upon the cost-effectiveness of venetoclax compared with ibrutinib and agreed that because of the substantial uncertainties in the magnitude and direction of benefit with venetoclax, the Committee could not come to a conclusion on the cost-effectiveness on venetoclax. pERC agreed with the CGP and pCODR Economic Guidance Panel (EGP) that the limitations in the available non-randomized clinical evidence for venetoclax and the absence of long-term data on the potential benefit gained with venetoclax in this setting compared with ibrutinib made it challenging to determine what the true incremental cost-effectiveness ratio may be. pERC acknowledged the EGP's struggle to provide reanalysis estimates and agreed that in the absence of robust direct or indirect clinical trial evidence, it is challenging to determine appropriate inputs for PFS and OS. pERC noted that inputs for efficacy and safety used in the submitted economic analysis were based on a match-adjusted indirect comparison between venetoclax and ibrutinib. Given limitations identified in the methodology used to match the patient populations, the EGP attempted to capture these uncertainties using one-way scenario analyses. Based on this, the EGP's scenario analyses suggested that, compared to the appropriate albeit expensive comparator ibrutinib, venetoclax could be dominant (less costly and more effective), more costly and more effective, or less costly and less effective (i.e., mostly spread across three quadrants of the cost-effectiveness plane). pERC therefore agreed with the EGP's conclusion that in the absence of robust direct or indirect evidence, the magnitude and direction of the incremental benefit and incremental cost with venetoclax remain uncertain and therefore it is difficult to determine what the cost-effectiveness of venetoclax may be. pERC also noted that there were no evidence (i.e., estimates or analyses) provided to address the cost-effectiveness of venetoclax in patients who have already been treated with ibrutinib or

idelalisib plus rituximab. Therefore, the Committee could not deliberate on the cost-effectiveness of venetoclax in this population.

pERC considered the feasibility of implementing a reimbursement recommendation for venetoclax and noted several factors. pERC noted the absence of evidence (completed or ongoing trials) evaluating the comparative effect of venetoclax against currently available standard treatment options. However, the Committee felt there was a sufficient number of patients with the del(17p) who could have been randomized to venetoclax and to relevant treatment options at the time the M13-982 trial was being conducted. pERC noted that the current review is for the use of venetoclax as monotherapy in patients who have relapsed or refractory CLL and del(17p) mutation status. Therefore, it is beyond the scope of this review to comment on the efficacy and safety of venetoclax as a combination therapy or use in the front-line setting in patients with the del(17p) mutation. pERC noted that concerns remain regarding TLS with the use of venetoclax and, therefore, intensive monitoring and prophylactic measures are required to prevent TLS in patients, particularly in the ramp-up stage of treatment, in which patients may need to be periodically hospitalized. Patients would therefore need to be within close proximity of a hospital for the first month of therapy.

pERC considered factors affecting the budget impact and noted that the front-line CLL population is large, but the number of patients with the del(17p) is a smaller subgroup. However, pERC noted that the incidence of del(17p) mutations increases as patients progress through treatments, and it is therefore expected that the number of eligible patients, and potential budget impact, will increase as patients progress between therapies. pERC therefore agreed that the potential budget impact of venetoclax is uncertain but likely to be high.

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
- Guidance from the pCODR clinical and economic review panels
- Input from two patient advocacy groups (Lymphoma Canada and the CLL Patient Advocacy Group)
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the safety and efficacy of venetoclax (Venclexta) as compared with an appropriate comparator in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) and who harbour the 17p deletion.

Studies included: Non-comparative trial, active comparators available

The pCODR systematic review included one open-label, non-randomized trial, study M13-982, that evaluated the use of venetoclax in patients with relapsed or refractory CLL harbouring the 17p deletion [del(17p)]. Key inclusion criteria included age ≥ 18 years, diagnosis with relapsed or refractory CLL harbouring del(17p) in > 7% of cells in peripheral blood, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2, a creatinine clearance ≥ 50 mL/min, and adequate coagulation and hepatic function. Notably, patients were not excluded based on prior ibrutinib or idelalisib plus rituximab therapy. The trial protocol included prophylactic measures for tumour lysis syndrome (TLS). Venetoclax dosing began with a five-week ramp-up dosing schedule starting at 20 mg per day, and then increasing each week to 50 mg, 100 mg, 200 mg, and finally 400 mg. Patients continue to receive 400 mg of venetoclax once daily until disease progression or unacceptable toxicity.

The pCODR review also provided contextual information on preliminary results from the M14-032 trial. The trial included 64 patients randomized into parallel arms based on prior treatment with ibrutinib or idelalisib plus rituximab. Among the 64 patients in the trial, 23 had the del(17p) mutation and were evaluated for efficacy and safety following treatment with venetoclax. Based on interim results that have been published as a poster, overall response rate was 65% in the subgroup of patients with del(17p). Results are not available for any other outcomes. pERC considered the results presented as part of this ongoing trial and agreed that they were preliminary. pERC noted that the promising results observed will need confirmation through mature results that are peer-reviewed and published. Based on this limitation, the Committee concluded that it could not determine the efficacy and safety of using venetoclax in this select group of patients.

Patient populations: Most patients naive to previous treatment with ibrutinib or idelalisib plus rituximab

The majority of patients entered into the M13-982 trial were male (n = 61.5%) and Caucasian (97.3%), had an ECOG PS of 0-1 (92.6%). The median age of patients was 67. A total of five patients had prior therapy with ibrutinib or idelalisib. The median number of prior therapies was two (range one to six).

Key efficacy results: Improved overall response rate, immature progression-free survival, and overall survival

The key efficacy outcomes deliberated on by pERC in the M13-892 trial was overall response rate (ORR), the primary outcome of the trial. Key secondary outcomes included progression-free survival (PFS), overall survival (OS), quality of life (QoL), and safety. An ORR of 79% was detected in the main cohort (n = 107), with eight (7.5%) patients achieving a complete response. Medians were not reached for PFS, OS, duration of response, and a number of other secondary outcomes at the time of the data analysis.

pERC considered the available evidence in this setting and acknowledged that the current data suggest there is anti-tumour activity with venetoclax. pERC also considered the availability of effective treatment options in this setting — notably ibrutinib and, more recently, idelalisib plus rituximab — and acknowledged the absence of robust direct or indirect clinical evidence to assist with drawing a conclusion on venetoclax relative to currently available therapies. The Committee considered the strength of the evidence and agreed that significant limitations remained due to the lack of comparative evidence and absence of long-term data on outcomes important to decision-making (such as OS and PFS). Overall, the Committee was not satisfied that the available evidence clearly demonstrated a net overall clinical benefit of treatment with venetoclax.

Patient-reported outcomes: Clinically meaningful improvement in quality of life from baseline to week 24; relative improvement unknown

Patient-reported outcomes were evaluated in the M13-982 study using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire–Chronic Lymphocytic Leukemia 16 (QLQ-CLL16). The trial evaluated clinical relevance based on the minimally important difference (MID) of values from baseline to week 24. Significant changes from baseline were not evident in cognitive functioning or in the following items related to physical functioning: nausea, vomiting, pain, appetite loss, constipation, or diarrhea. Scores from the QLQ-CLL16 demonstrated significant improvements in disease effects, social problems, and future health worries, which exceeded the MID at all time points up to 24 weeks and including weeks 36 and 48. Improvements in treatment side effects were reported as statistically significant; however, they did not exceed the MID in the first 24 weeks. pERC agreed that in a treatment setting in which patients would receive treatment until disease progression or unacceptable toxicity, MIDs based on a change from baseline until week 24 may not capture the full impact of venetoclax on patients' QoL throughout treatment. Additionally, given the availability of effective treatment options in this setting, pERC noted that the absence of comparative evidence made it challenging to determine the comparative impact of venetoclax on patients' QoL versus other available therapies.

Safety: Management for tumour lysis syndrome

pERC discussed the safety profile of venetoclax and noted it to be generally well tolerated, with manageable toxicities. Grade ≥ 3 adverse events included neutropenia (40%), infection (20%), anemia (18%), and thrombocytopenia (15%). Serious adverse events included autoimmune hemolytic anemia (7%), pneumonia (6%), and febrile neutropenia (5%). pERC noted that concerns about tumour lysis syndrome were addressed in the trial. Based on appropriate risk assessment for TLS (by dividing patients into low, medium, and high risk for TLS), preventive measures, and intensive monitoring, the risk of laboratory TLS in the M13-982 trial was seen to be low (5%). Among the five patients who developed laboratory evidence of TLS, three continued treatment without interruption and the remaining two patients required a one-day dose interruption before resuming therapy. Laboratory TLS resolved in all cases without clinical sequelae. pERC however acknowledged that patients may periodically need hospitalization during the first month of treatment to appropriately manage potential toxicities during the ramp-up phase of treatment. Therefore patients would need to be within close proximity of a hospital for the first month of therapy. Overall, pERC concluded that the adverse events with venetoclax were considered to be manageable; however, intensive monitoring and management are required to minimize the risk of TLS in patients.

Comparator information: Absence of robust indirect evidence

pERC noted that ibrutinib and, more recently, idelalisib plus rituximab are effective standard treatment options available to Canadian patients in this setting. Given the absence of direct comparative trials evaluating the safety and efficacy of venetoclax compared with these relevant treatment options, an indirect treatment comparison was done for venetoclax versus ibrutinib. A match-adjusted indirect comparison was conducted to control for important variables that may have an impact on treatment effect. Point estimates from the analyses suggested that venetoclax is similarly as efficacious as ibrutinib in terms of PFS and OS. However, pERC noted that limited information is available on the methodology and results of this indirect comparison, as the data are pending peer-review and publication. Therefore, only a limited critical appraisal of the methodology and results of the indirect comparison could be completed, and pERC agreed that great caution should be used in drawing conclusions based on these indirect data. Overall, in the absence of robust direct or indirect clinical evidence, pERC was, therefore, unable to come to a conclusion on the comparative efficacy of venetoclax and ibrutinib.

Need and burden of illness: Need in patients with the del(17p)

CLL is a common leukemia with a long natural history. Each year, approximately 2,400 Canadians are diagnosed and 650 die from CLL, 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 cytogenetics as del17p, or 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. The outlook for the subgroups of patients who have CLL and high-risk disease (del(17p)) is especially poor, as the presence of these mutations is associated with resistance to standard chemoimmunotherapy, and more effective agents with activity in this biologically aggressive subgroup are needed. In previously untreated patients, the incidence of the TP53 gene abnormalities is approximately 10% to 12% (detected by interphase FISH cytogenetics as del(17p) in 5% to 7% or by sequencing the gene mutation in 3% to 5% of patients). In the relapsed or refractory setting, through the process of clonal evolution, the incidence of TP53 abnormalities can increase up to approximately 30%. Most Canadian cancer centres have access to FISH testing and thus are able to identify patients with del(17p). However, few centres have routine access to TP53 gene mutation analyses, representing an important gap. New therapies have recently become available for the treatment of newly diagnosed or relapsed or refractory patients who have CLL and the del(17p). The current standard of treatment for these patients following at least one prior systemic regimen is ibrutinib or idelalisib plus rituximab. For patients who develop resistance or intolerance to available tyrosine kinase inhibitors, there is currently no effective alternative therapy and prognosis is very poor. Therefore, pERC agreed that there is a need for additional effective therapies for patients who have CLL and the del(17p) mutation, which provide improvements in survival, have more favourable toxicity profiles, and improve QoL.

Registered clinician input: Need in patients who have progressed on ibrutinib or idelalisib plus rituximab

According to registered clinician input, venetoclax provides another treatment option for CLL patients with the del(17p) status and who have failed all other treatments or who cannot tolerate or have contraindications to other available treatments. Clinicians providing input indicated that venetoclax is superior to any other available therapy for patients who have failed a kinase inhibitor (ibrutinib or idelalisib), including patients with and without del(17p), but noted that there are no direct comparative data to suggest whether venetoclax is superior or equivalent to the novel kinase inhibitors (ibrutinib and idelalisib). Based on the preliminary evidence available for patients who have previously been treated with ibrutinib or idelalisib plus rituximab, pERC agreed that venetoclax is a promising treatment option. Although the Committee agreed that there is a significant need for treatment options in this setting, it was unable to overcome the considerable uncertainty in the preliminary results of an ongoing trial to draw a conclusion on the magnitude or direction of effect in these patients. In considering the results of the M13-982 trial, pERC acknowledged that the data suggest there is anti-tumour activity with venetoclax. However, significant limitations remained due to the lack of comparative evidence and absence of long-term data on outcomes important to decision-making (such as OS and PFS). The Committee was not satisfied that the available evidence clearly demonstrated a net overall clinical benefit of treatment with venetoclax in patients who are eligible for current therapies (e.g., ibrutinib or idelalisib plus rituximab) or in patients who may have a intolerance or contraindication to currently available treatments.

PATIENT-BASED VALUES

Values of patients with chronic lymphocytic leukemia: Symptom management, quality of life improvement, and treatment option

pERC deliberated upon patient advocacy group input for venetoclax and discussed the values of patients with previously treated CLL and who harbour the del(17p). Patients reported minimal symptoms with early-stage disease; however, QoL is affected with advanced disease. Patients experience stress from the diagnosis, anxiety, difficulty sleeping, and depression. Symptoms that have the most impact on day-to-day living are fatigue and/or lack of energy, followed by increased lymphocyte count, enlarged lymph nodes, and frequent infections. Among 248 patients providing input, at least 70% indicated that frequent infections, fatigue, viral reactivation, low platelet count, increasing lymphocyte counts, and anemia were very important disease symptoms to control. Patients described being devoid of energy and stated that they needed to rest often in order to perform their normal daily activities. All symptoms were described as interfering with patients' performance, ability to work, travel, and day-to-day-activities. Caregivers indicated that CLL has a profound impact on them, in that they have experienced stress due to diagnosis,

anxiety, difficulty sleeping, and depression. Caregivers face emotional and psychological burdens. Caregivers also deal with performing exhausting caretaking duties, transportation duties, accompanying patients to time-consuming and distant medical appointments, taking notes during clinic visits, purchasing drugs and dietary supplements, and ensuring doctors' instructions are followed. They also face accessibility issues in relation to financial burden and travel distance to access the drug.

pERC noted that QoL improvements were reported in the M13-982 trial from baseline up to week 24. The Committee, however, noted that it would be important to know the impact of venetoclax on patients' QoL beyond week 24, as treatment would be continued until progression or unacceptable toxicities. Given the absence of comparative evidence, pERC was unable to determine the comparative safety of venetoclax in light of currently available standard treatment options The Committee was therefore unable to determine whether or not venetoclax aligned with value patients stated about the importance of having treatment options that are able to better manage key disease-related side effects. pERC also noted that, as an oral treatment, venetoclax may offer more accessible treatment and therefore, align with values of patients and caregivers. pERC, however, noted that patients may periodically need hospitalization during the first month of treatment with venetoclax to appropriately manage potential toxicities during the ramp-up phase of treatment therefore patients would need to be within close proximity of a hospital for the first month of therapy.

Patient values on treatment: Treatment option, ease of administration, quality-of-life improvement

Patients providing input had received a variety of treatments in the first-line setting and were at various stages of their treatment course (first- to fourth-line). Among 71 patients receiving second-line treatment, 22 received ibrutinib, 15 rituximab, seven fludarabine/rituximab/ cyclophosphamide, and five bendamustine/rituximab. Patients describe both positive and negative side effects of current treatment. Among 248 patients providing input, more than 40% indicated that they would be willing to tolerate fatigue, cough, diarrhea, nausea, and fever as a short-term side effect if it resulted in improvements in QoL. More than 40% of these patients, however, indicated that TLS and breathing difficulties or pneumonia were side effects that they would be unwilling to tolerate in the short term. In general, patients seek new therapies that produce quick, favourable outcomes with relatively mild side effects compared with existing treatments. Patients however do acknowledge that venetoclax therapy carries risks of serious side effects, but given that they will not respond to other treatments because of their genetic profile, they are willing to tolerate those risks in the hope of having a treatment that extends their life. Among 34 to 36 patients who described the most important symptoms of their disease they would like to have controlled with new therapies, more than 83% to 87% rated that QoL, disease and side effect control, longer survival, improved blood counts, and disease remission as very important. Patients also indicated that they are mostly able to access treatments locally within their communities (111/137 providing input; 81%). The majority of patients (228/248 providing input; 92%) also indicated that it is very important for them and their consulting physician to choose among options when selecting treatment.

Among patients providing input, 20 had direct experience with venetoclax, nine of whom had the del(17p). Among six patients reporting on their experience with venetoclax, five indicated that it managed all their symptoms. These six patients also indicated that it managed the following: increasing lymphocyte counts (n = 5), enlarged spleen (n = 4) and enlarged lymph nodes and fatigue or lack of energy (n = 3 each). Among one to 13 patients providing input, discomfort due to enlarged spleen, fever, white blood cell counts, enlarged lymph nodes, night sweats, chills, and red blood cell counts were disease symptoms that were most improved with venetoclax.

pERC deliberated upon the alignment of venetoclax with patient values and noted that based on the results of the M13-982 trial, venetoclax provides another oral treatment option with a manageable toxicity profile. However, the Committee noted that TLS was reported in five patients in the M13-982 trial, an adverse event that patients indicated they would be unwilling to have as part of a new treatment. TLS was managed through risk assessment and stringent measures for prophylaxis that were part of the trial design and none of the patients who experienced TLS discontinued treatment. pERC however acknowledged that patients may periodically need hospitalization during the first month of treatment to appropriately manage potential toxicities during the ramp-up phase of treatment. Therefore patients would need to be within close proximity of a hospital for the first month of therapy. pERC also discussed the lack of comparative evidence on the efficacy and safety of venetoclax against currently available standard treatment options, and the absence of long-term follow-up data to understand the

impact of venetoclax on patient-important outcomes such as PFS and OS led pERC to conclude that venetoclax only partially aligned 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 ibrutinib in patients with CLL who have received at least one prior therapy, and who have the del(17p) mutation.

Basis of the economic model: Clinical and economic inputs

Costs considered in the economic model included drug costs, drug administration costs, adverse event costs (including TLS), and routine care 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 a match-adjusted indirect comparison of venetoclax and ibrutinib, which suggested similar efficacy between the two treatments. pERC acknowledged considerable limitations in the results of this analysis and agreed that caution should be used in interpreting the results.

Drug costs: High drug cost, treatment until disease progression

Venetoclax costs $6.80 per 10 mg, $33.99 per 50 mg and $67.99 per 100 mg. At the recommended ramp-up and subsequent doses, venetoclax costs $62.89 per day and $1,760.88 per 28-day course for first cycle (ramp-up). For all subsequent cycles, venetoclax costs $271.95 per day and $7,614.60 per 28-day course. The recommended ramp-up dose for venetoclax includes:

- Week 1: 2 × 10 mg daily
- Week 2: 1 × 50 mg daily
- Week 3: 1 × 100 mg daily
- Week 4: 2 × 100 mg daily

All subsequent doses are:

- Week 5 and onward: 4 × 100 mg daily

Ibrutinib costs $90.65 per 140 mg capsule. At the recommended dose of 420 mg once daily, ibrutinib costs $271.95 per day and $7,614.60 per 28-day course.

Cost-effectiveness estimates: Unable to draw a conclusion on cost-effectiveness

pERC deliberated upon the cost-effectiveness of venetoclax compared with ibrutinib. pERC noted the absence of long-term data on the results of the M13-982 trial, limitations associated with the match-adjusted indirect comparison between venetoclax and ibrutinib and agreed with the CGP and EGP that considerable uncertainty remained in the incremental benefit conferred with venetoclax. pERC acknowledged the EGP's struggle to provide reanalysis estimates and agreed that in the absence of robust direct or indirect clinical trial evidence, it is challenging to determine appropriate inputs for PFS and OS. The EGP attempted to capture the uncertainty related to the inputs for PFS and OS by using the 95% confidence interval on the hazard ratio obtained through the match-adjusted indirect comparison. Based on this, the EGP's scenario analysis indicated that the cost-effectiveness ratio for venetoclax could be dominant (less costly and more effective), more costly and more effective, or less costly and less effective (e.g., mostly spread across three quadrants of the cost-effectiveness plane). pERC therefore agreed with the EGP's conclusion that the magnitude and direction of benefit with venetoclax remains uncertain. Therefore, the Committee was unable to determine what the cost-effectiveness of venetoclax compared with ibrutinib may be. pERC also noted that there were no estimates provided to address the cost-effectiveness of venetoclax in patients who have already been treated with ibrutinib or idelalisib plus rituximab. Therefore, the Committee could not deliberate on the cost-effectiveness of venetoclax in this specific subgroup population.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Potentially large budget impact
pERC considered the feasibility of implementing a reimbursement recommendation for venetoclax and noted several factors, including PAG's concerns over the lack of evidence comparing venetoclax to ibrutinib or idelalisib plus rituximab. pERC stressed this concern throughout its deliberations and agreed that it was unable to draw a conclusion regarding the net clinical benefit of venetoclax compared with available effective treatment options. In addition, pERC agreed that this lack of evidence created considerable uncertainty regarding the cost-effectiveness estimates. pERC also noted the number of patients recruited on the M13-982 trial, and other trials that have randomized similar numbers of patients with the del(17p). The Committee felt that a sufficient number of patients with the del(17p) was available to conduct a randomized trial of venetoclax and relevant treatment options at the time the M13-982 trial was being run. pERC noted that the current review is for the use of venetoclax as monotherapy in patients with relapsed or refractory CLL and who have the del(17p) mutation status. Therefore, there is currently no evidence to comment on the efficacy and safety of venetoclax as a combination therapy or use in the front-line setting. 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.

pERC agreed that venetoclax's oral route of administration creates ease of administration for patients and is an enabler to implementation, but pERC acknowledged that patients may periodically need hospitalization during the first month of treatment to appropriately manage potential toxicities during the ramp-up phase of treatment. Therefore patients would need to be within close proximity of a hospital for the first month of therapy. pERC considered factors affecting the budget impact and noted that the front-line CLL population is large, but the number of patients with the del(17p) is a smaller subgroup of patients. pERC noted that the incidence of del(17p) mutations increases as patients progress between treatments and therefore it is expected that the number of eligible patients, and potential budget impact, will increase as patients progress between therapies. 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.

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) in patients with the del(17p) status
Burden of Illness	• CLL is the most common leukemia in Western countries • In Canada in 2010, the latest year for which statistics are available, 2,195 patients were diagnosed with CLL and 600 died of it
Current Standard Treatment	• Ibrutinib • Idelalisib plus rituximab
Limitations of Current Therapy	• No effective treatment options in patients who have failed prior treatment with ibrutinib or idelalisib plus rituximab • Intolerance or contraindication to current standard treatments in some patients

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. Paul Hoskins, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy Thompson, Pharmacist
Valerie McDonald, Patient Member Alternate
Carole McMahon, Patient Member
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Dr. Marianne Taylor, Oncologist
Danica Wasney, Pharmacist

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

- Valerie McDonald, who did not vote due to her role as a patient member alternate
- Scott Berry and Kelvin Chan, who were not present.

Avoidance of conflicts of interest

All members of pERC 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, nine members had a real, potential or perceived conflict and 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 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*.

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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