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:
Ibrutinib (Imbruvica)

Submitted Funding Request:
For the treatment of patients with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy.

Submitted By:
Janssen Inc.

Manufactured By:
Janssen Inc.

NOC Date:
April 25, 2016

Submission Date:
April 22, 2016

Initial Recommendation Issued:
September 1, 2016

pERC RECOMMENDATION	pERC does not recommend reimbursement of ibrutinib for the treatment of patients with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy. The Committee made this recommendation because it was unable to conclude that, based on the available evidence, there is a net clinical benefit of ibrutinib compared with appropriate comparators. While pERC noted that there is a need for effective treatments in this setting and that ibrutinib produces anti-tumour activity, the Committee concluded that there was considerable uncertainty in the magnitude of clinical benefit compared with appropriate comparators in regard to outcomes important to decision-making, such as overall survival, progression-free survival, and quality of life. Despite the absence of comparative evidence, based on the quality of patient input from patient advocacy groups and the activity of ibrutinib, pERC acknowledged that ibrutinib's ability to control disease symptoms, bring about improvements in quality of life, and provide ease of administration all aligned with patient values. The Committee concluded that, at the submitted price, ibrutinib is not cost-effective in patients with WM who have had at least one prior therapy. pERC also noted that there is a potential for a substantial budget impact with ibrutinib.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**No next steps**

SUMMARY OF pERC DELIBERATIONS

WM (also known as lymphoplasmacytic lymphoma [LPL]) is an indolent non-Hodgkin lymphoma. WM is an uncommon disease with an incidence of 3 to 5 per million in the United States. Approximately one-third of patients with WM are asymptomatic at presentation. While survival in patients with WM is dependent on prognostic factors present at initial diagnosis, median survival is 5 years. Based on factors specified by the WM International Prognostic Scoring System (IPSS) that affect the median survival, patients with low-, intermediate-, and high-risk disease have a median of 12, eight, and four years' survival, respectively. Current treatment of WM upon relapse or progression depends on agents used in initial treatment, and whether re-treatment with rituximab is considered appropriate (generally, for those with previous response to rituximab-based therapy and with disease progression that occurred more than 12 months following their last rituximab administration). Based on a review of available literature for therapies for relapsed WM, response rates of 60% to 80% may be expected with combination therapies and 30% to 80% with single agents, with a progression-free survival (PFS) duration of approximately 12 to 16 months. pERC agreed that treatment options with demonstrated benefit over available treatment options in terms of symptom control, improvement in quality of life and longer remission rates are a continued need for patients.

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

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

pERC deliberated upon the results of two non-comparative studies: PCYC-1118, a single-arm study; and the non-randomized arm (Arm C; a companion sub-study) of study PCYC-1127, which evaluated ibrutinib in patients with WM who have received at least one prior therapy. The Committee was not satisfied that the available evidence clearly demonstrated a net overall clinical benefit of treatment with ibrutinib. pERC acknowledged that although a standard treatment option is not available in this setting, outcomes observed with ibrutinib in terms of objective response and PFS were similar to those seen in the literature with currently available treatments. Additionally, complete response was not observed in any patients and only partial, very good partial and minor responses were reported. pERC acknowledged that the current evidence suggests that there is anti-tumour activity with ibrutinib; however, the magnitude of effect compared with available therapies was uncertain given the lack of comparative data and long-term outcome data on outcomes important to patients such as overall survival and PFS. pERC further considered the randomized components of study PCYC-1127 (Arms A and B of the study) and agreed that it would have been feasible to conduct a randomized controlled trial versus available treatment options. While pERC considered that the objective response rate and PFS observed with ibrutinib in the two trials to be important, pERC felt it was not sufficient evidence of effectiveness and only limited conclusions could be drawn from the two small non-comparative studies. pERC noted that it has accepted evidence from non-comparative studies in previous submissions for reasons that are context (drug and disease) specific; however, in this instance, given the absence of a clear advantage over available treatment options, the feasibility of conducting a randomized trial in this disease setting, the short trial follow-up, and a lack of complete responses to treatment, the Committee was unable to draw a conclusion on the comparative effectiveness of ibrutinib in this patient population.

In addition, pERC noted that the quality of life results reported in Arm C of the PCYC-1127 study suggested that quality of life is at least maintained. Given the small number of patients in the analysis and limited reporting of full results, only limited interpretation could be made regarding these patient reported outcomes. pERC agreed that the toxicity profile of ibrutinib, despite the high incidence of grade 3 or higher neutropenia and thrombocytopenia, was reasonable and manageable. Specific adverse events of interest such as bleeding, infections, atrial fibrillation and hypertension were observed in patients and would require monitoring. Additionally, drug-drug interactions are of concern with the use of ibrutinib, given the mechanism of action of the drug.

pERC considered input provided by patient advocacy groups for ibrutinib and commended the quality and quantity of data available within the input. Given that the clinical trial evidence presented as part of the review had a combined total of 91 patients, pERC was impressed with the comparatively large number of

patients with WM recruited by the patient advocacy groups to participate in the surveys (n=436) and with the number of patients with experience using ibrutinib (n=115). Especially in the absence of robust clinical evidence, pERC expressed appreciation for the extent of the patient input and equanimity in deliberating on patient input that clearly conveyed the expectations and experiences of patients with ibrutinib. Patients with WM valued treatments that bring about remission, control disease symptoms, provide survival benefit, improve blood counts, and improve quality of life. pERC considered the clinical trial evidence with the information provided through patient input and struggled to reconcile the experiences of individual patients described in the patient group input with the pooled clinical trial data on patients' experiences. Consideration was also given to whether patients reporting their experiences as part of the patient group input may have comprised a self-selected population that was well enough to provide input. This possibility was highlighted in the misalignment of quality-of-life data from Arm C of the PCYC-1127 trial, which indicated no change in quality of life compared with the experiences patients reported through the patient group input indicating improvements in quality of life. The Committee had a robust discussion on the alignment of ibrutinib with patient values and various opinions were expressed throughout the meeting. While pERC was unable to draw a conclusion on the comparative effect of ibrutinib (with available treatment options) on patient values, pERC acknowledged that ibrutinib's ability to control disease symptoms, bring about improvements in quality of life, and provide ease of administration all aligned with patient values, based on the high quality patient input from Patient Advocacy Groups and the activity of ibrutinib. Overall, pERC concluded that ibrutinib aligns with patient values.

pERC deliberated upon the cost-effectiveness of ibrutinib and concluded that ibrutinib is not cost effective. Due to limitations in the available non-randomized clinical evidence for ibrutinib and the absence of long-term data on the potential survival benefit gained with ibrutinib in this setting, pERC concluded that it was challenging to determine the true incremental cost-effectiveness ratio (ICER). pERC acknowledged the pCODR Economic Guidance Panel (EGP's) struggle to provide re-analysis estimates and agreed that in the absence of robust direct or indirect clinical trial evidence, it is challenging to determine an appropriate input for the long-term OS and treatment costs. pERC however agreed that it is inappropriate to extrapolate long term-survival using a mortality rate from an age adjusted healthy population as there is insufficient evidence to suggest that ibrutinib provides such a survival advantage. pERC agreed that this limitation created the largest uncertainty in the ICER. pERC also agreed that based on the age and disease course of patients, it would not be appropriate to model a 20-year time horizon as done in the base case, and agreed with the EGP's use of a five-year time horizon. pERC noted that in a one way sensitivity analysis conducted by the EGP that changed the time horizon to five-years, the ICER more than doubled from the base-case results. Overall, despite the limitations in the clinical evidence, pERC agreed that ibrutinib is not cost-effective.

pERC discussed the feasibility of implementing a reimbursement recommendation for ibrutinib for patients with previously treated WM. pERC noted that there was no evidence available on the efficacy and safety of ibrutinib plus rituximab combination therapy. Arms A and B of the randomized portion of study PCYC-1127 are expected to provide data on this combination treatment both in the newly diagnosed and previously treated settings. pERC further acknowledged that the current evidence, from small non-randomized studies, was not sufficient to conclude that there was a net clinical benefit with ibrutinib in the previously treated setting.

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 provides clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from pCODR clinical and economic review panels
- Joint Input from two patient advocacy groups, Lymphoma Foundation Canada and Canadian Organization for Rare Disorders
- Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of ibrutinib compared to appropriate comparators in the treatment of adults with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy.

Studies included: Two non-comparative studies

The pCODR systematic review included two non-comparative studies: one non-randomized study (PCYC-1118E) and one non-randomized sub-study (Arm C) from within the randomized PCYC-1127 study.

- PCYC-1118E is a phase 2, open-label, multi-centre, single-arm study that administered ibrutinib to patients with WM who have had at least one prior therapy. Key eligibility criteria included the need for treatment according to consensus guidelines and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 2. Patients with central nervous system lymphoma or clinically significant cardiovascular disease, taking warfarin, or taking drugs that prolonged QT interval were excluded.
- PCYC-1127 is an ongoing study with three treatment arms. Arms A and B pertain to the randomized portion of the study, which evaluated ibrutinib plus rituximab combination therapy compared with rituximab. These arms remain blinded and no results are yet available. Notably, more than half the patients in arms A and B were previously treated. Arm C was a non-randomized sub-study. Key inclusion criteria for Arm C of PCYC1127 required that patients have symptomatic WM, ECOG PS ≤ 2, and disease that is refractory to last prior rituximab-containing therapy (defined as relapse after < 12 months since last rituximab dose) or failure to achieve at least a minor response after last rituximab-containing therapy.

pERC noted that the two available studies on the use of ibrutinib in this disease setting were small non-randomized non-comparative studies. pERC acknowledged that WM is an uncommon disease and discussed whether recruiting patients into a randomized study would be feasible. Given that arms A and B of study PCYC-1127 were randomised, and taking into consideration the exceptional number of patients the patient advocacy groups were able to recruit in their input, pERC agreed that a randomized study would have been feasible in this disease setting. pERC commended the effort made by the patient advocacy groups in order to provide information on the experiences of patients and caregivers.

The pCODR review also provided contextual information on literature that provided data on relevant comparators for treatment of adults with Waldenström's macroglobulinemia who have received at least one prior therapy. A summary was presented, from the European Medicines Agency 2015 Assessment Report for ibrutinib in WM, which provided context for the results from studies PCYC 1118E and PCYC-1127. Based on this evidence, objective response rates (ORRs) with single agents ranged from 51.4% to 85%, duration of responses ranged from 10 to > 20 months, and median progression-free survival (PFS) ranged from 12 to 16 months. Additional literature on relevant comparators (single-agent and combination regimen using bendamustine) were provided. In studies using combination treatment ORR was 80.2%-83.3%, with major response observed in 74.6% of patients. In the absence of evidence to inform the comparative efficacy of ibrutinib to available treatment options, pERC relied on the evidence provided through the literature to inform its deliberations. pERC therefore agreed that the response rates observed in the literature are similar in magnitude to those observed with ibrutinib.

Patient populations: Eastern Cooperative Oncology Group Performance Status 0 to 1

PCYC-1118E enrolled 63 patients with a median age of 63 (range: 44 to 86); 47 patients (75%) had ECOG PS of 0, and 16 patients (25%) had ECOG PS of 1 to 2. The median number of previous therapies was two (range: 1 to 9). The most common previous therapies were monoclonal antibody (90%), glucocorticoid (67%), proteasome inhibitor (52%), and alkylator (51%). Prior rituximab use was not reported. Based on the International Prognostic Scoring System (IPSS), patients had low (22%), intermediate (43%), and high (35%) scores. Eighty-nine per cent of patients had the $MYD88^{L265P}$ mutation. The median time from diagnosis of WM was approximately six years (76 months, ranging from six to 340).

Arm C of PCYC-1127 enrolled 31 patients with a median age of 67 (range: 47 to 90). Twenty-five patients (81%) had ECOG PS of 0 to 1 and 6 patients (19%) had ECOG PS of 2. The median number of previous therapies was four (range: one to eight). All patients in the study had previously received rituximab. The most common previous therapies, apart from rituximab, were a glucocorticoid (81%), an alkylator (81%), a proteasome inhibitor (45%), or a purine analogue (42%). Twenty-nine per cent of patients had progression on or within 60 days of their last therapy; an additional 29% had no response (stable disease or disease progression) to their most recent therapy. Based on the IPSS, patients had low (23%), intermediate (35%), and high (42%) scores. Three patients were enrolled at two Canadian sites (Montreal, Halifax).

Patients in both studies were given ibrutinib, 420 mg daily, until disease progression or unacceptable toxicity. In study PCYC-1118, at a median follow-up of 14.8 months, 43 patients remained on ibrutinib and 20 had discontinued therapy (10 for treatment failure, two for bleeding, and eight for other reasons)

Key efficacy results: Progression free survival and objective response rate

The key efficacy outcomes deliberated on by pERC were ORR and PFS, the primary outcomes in the PCYC-1118 and PCYC-1127 studies, respectively. In study PCYC-1118E, the primary outcome was ORR which was reported to be 90.5% (95% confidence interval [CI], 80.4% to 96.4%]. Major response, defined as partial or very good partial response or > 50% reduction in serum immunoglobulin M (IgM) levels, was measured in 73% (95% CI, 60.3 to 83.4). At 18 months, median duration of response was not reached in the study (95% CI, 0.03 to 29 months). While median PFS and OS were not reached, PFS at two years was 69.1% (95% CI, 53.2% to 80.5%) and OS at two years was 95.2% (95% CI, 86.0% to 98.4%). In study PCYC-1127, the primary outcome was PFS as defined by the modified Consensus Response Criteria from the Sixth International Workshop on WM. Median PFS and OS were not reached, but at one year, PFS was 93% (95% CI not reported) in Arm C. ORR in Arm C was 90% (95% CI not reported). Major response rate, although not defined in study PCYC-1127, was 71% (95% CI not reported). Duration of response and OS were not reported. OS was not reported for study PCYC-1127.

pERC discussed the results observed in the two non-randomized data sets and agreed that the magnitude and direction of effect were similar between the two studies. pERC acknowledged that response rates and durations of response with ibrutinib are clinically meaningful, particularly in this heavily pre-treated patient population suggesting that ibrutinib is active in this setting. There was however no information to evaluate the efficacy of ibrutinib relative to various other treatment options available in this setting. pERC agreed that the response rate and PFS demonstrated with ibrutinib were similar to those reported in the literature. The Committee acknowledged that phase III data would have been more informative and agreed that a randomized study is feasible in this patient population. Furthermore, pERC noted that it has accepted evidence from non-comparative studies in previous submissions for reasons that are context (drug and disease)-specific; however, in this instance, given the absence of a clear advantage over available treatment options, the feasibility of conducting a randomized trial in this disease setting, the short trial follow-up, and a lack of complete responses to treatment, the Committee was unable to draw a conclusion regarding the comparative effectiveness of ibrutinib in this patient population.

Patient-reported outcomes: Limited results; at least maintenance of patient reported outcomes

Patient-reported outcomes (PROs) were available only in study PCYC-1127 and measured using the Functional Assessment of Cancer Therapy (FACT) scale for patients with anemia/fatigue (FACT-An) Total Score, Fact-An Anemia Subscale, and the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) visual analogue scale. Small changes from baseline were reported, but statistical comparisons were not provided, so the clinical significance of these results remains uncertain. Data on questionnaire completion rates and minimally important differences were not available. Although these results appear to suggest no decline in PROs with the use of ibrutinib in this patient population, pERC agreed that only limited interpretation could be

made regarding these PROs, given the small number of patients in the analysis and limited reporting of full results.

Safety: Although manageable, higher incidence of grade 3 and 4 adverse events

pERC discussed the toxicity profile of ibrutinib in the two studies. In PCYC-1118, 38% of patients experienced serious adverse events (SAE's). Grade 3 or higher adverse events (AE's) were experienced by 51% (n=32) of the patients in the study. The most common grade 3 or 4 AE's were neutropenia, followed by thrombocytopenia, pneumonia, anemia, atrial fibrillation, febrile neutropenia, pyrexia, abdominal pain, cellulitis, dehydration, and hypertension. Hemorrhagic AEs of any grade were experienced by 44.4% of patients. There was one report of grade 3 hematoma (post-procedural bleeding event) and all other bleeding events were grade 1 or 2. There were no grade 4 bleeding events. Atrial fibrillation was reported for five patients (three grade 1 to 2 and two grade 3). Among these, three events were related to ibrutinib. Dose discontinuation occurred due to atrial fibrillation, B-cell lymphoma, myelodysplastic syndrome, pleural effusion, post-procedural hematoma, and thrombocytopenia.

In PCYC-1127, 32% of patients experienced SAEs. Grade 3 or higher AEs were experienced by 65% (20) of patients. Common AEs (≥ grade 3) included neutropenia and hypertension, followed by anemia and diarrhea. There were no events of IgM flare or atrial fibrillation. No grade 3 or 4 bleeding events were reported. One patient discontinued ibrutinib because of gastrointestinal amyloidosis and another patient discontinued ibrutinib because of diarrhea. pERC agreed that the toxicity profile of ibrutinib, despite the high incidence of grade 3 or higher AEs, including neutropenia and thrombocytopenia, was reasonable and manageable. Specific AEs of interest, such as bleeding, infections, atrial fibrillation and hypertension, would require monitoring. Additionally, drug drug interactions are of concern with the use of ibrutinib, given the mechanism of action of the drug.

Need: Symptom control, longer remission rates and improved quality of life

WM (also known as lymphoplasmacytic lymphoma [LPL]) is an indolent non-Hodgkin lymphoma. WM is an uncommon disease with an incidence of 3 to 5 per million in the US. Approximately one-third of patients with WM are asymptomatic at presentation. Indications for therapy include complications related to IgM paraproteinemia and constitutional symptoms from anemia, hyperviscosity, adenopathy or hepatosplenomegaly, and neuropathy. The WM IPSS identifies five factors (age 65, hemoglobin < 11.6 g/L, platelets < 100 × 109/L, beta 2-microglobulin > 3.0 g/L, IgM paraprotein > 70 g/L) that have an impact on OS of patients. Increasing numbers of these factors are associated with shorter OS. Based on this, patients are classified as low risk (e.g., no to one risk factors, with the exception of age > 65 years), with a median survival of approximately 12 years (143 months); intermediate risk (two risk factors or > 65 years), with a median survival of eight years (99 months); and high risk (more than three factors), with a median survival of four years (44 months). Therefore, survival in patients with WM is variable (median five years), and depends on prognostic factors present at initial diagnosis as described above.

Current treatment of WM at relapse or progression depends on agents used in initial treatment, and whether re-treatment with rituximab is considered appropriate (generally, for those with progression more than 12 months following their last rituximab administration). pERC noted that while a standard option is not available, a variety of treatment options are currently used in this setting. Response rates of 60% to 80% may be expected with combination therapies and 30% to 80% with single agents, with PFS duration of approximately 12 to 16 months. Despite these response rates, pERC agreed that in this indolent disease, treatment options with demonstrated benefit over available treatment options in terms of symptom control, improvement in quality of life, and longer remission rates are a continued need for patients.

PATIENT-BASED VALUES

Values of patients with Waldenström's Macroglobulinemia: Symptom management and quality-of-life improvement

pERC considered input on ibrutinib provided by patient advocacy groups and commended the quality and quantity of data provided. Given that the clinical evidence presented as part of the review had a combined total of 91 patients, pERC was impressed with the comparatively large number of patients with WM recruited by the patient advocacy groups to participate in the surveys (n=436) number of patients with WM recruited by the Patient Advocacy Groups to participate in the surveys (n=436) and with the

number of patients with experience using ibrutinib (n=115). In the absence of robust clinical evidence, pERC expressed great satisfaction in deliberating on patient input, as it clearly conveyed the expectations and experiences of patients with ibrutinib.

Patients experience various impacts on their quality of life with WM. Among 299 survey respondents, 126 (42.9%) reported tiredness and/or lack of energy to have a significant impact. Additionally, tingling or numbness in feet or legs (26.9%), weakness (23.3%), shortness of breath (19.9%), joint or muscle pain (15.8%), swollen lymph nodes (15.0%), heavy night sweats (14.8%), and frequent infections (14.4%) also affect patients' quality of life. More specifically, symptoms of disease had a significant impact on patients' ability to work (34.6%), travel (28.0%), exercise (27.9%), volunteer (25.9%) and contribute financially to household (22%).

Patients experience with current therapy varied. Among 240 respondents, 63.4% felt that their current therapy was able to adequately manage their disease symptoms. However, at least 36.3% stated that they had relapsed after previous treatments (15% of respondents did not know whether they had relapsed). The number of prior treatments received varied with 85% of patients receiving one prior treatment, 79% more than one drug therapy, 64% three or more types of drugs and 18% receiving five or more types of drugs for their WM. Among 279 respondents, the most used prior therapies were rituximab alone or maintenance (33.7%) and bendamustine or bendamustine plus rituximab (22.2%). Among 86 Canadian respondents, 22.1% reported experiencing difficulty accessing treatment including having to travel great distances to receive treatment; meet specific provincial drug funding criteria, and pay out-of-pocket costs for treatments and associated travel.

Caregivers reported that their ability to travel, spend time with family and friends, volunteer, work, concentrate, and contribute financially to household expenses, as well as ability to attend to household chores and fulfill family obligations are most affected.

Patient values on treatment: Improved overall survival, slower disease progression, and availability of additional treatment options with new therapy

Patients indicated that they seek new therapies that produce quick and favourable outcomes with relatively mild side effects. Although most patients felt their current therapies were working to manage their symptoms, they anticipate their symptoms and disease will return. Patients indicated that they expect ibrutinib will bring about remission, control disease symptoms, allow them to live longer, improve blood counts and improve quality of life. Patients noted that the ability to take ibrutinib at home is important as it contributed to ease of administration for patients who live far from hospitals and may lower risk of contracting hospital acquired infections.

Among patients providing input, 115 had experience using ibrutinib with 88.6% having received at least one prior therapy before receiving ibrutinib. Among patients receiving ibrutinib following at least one prior treatment, 90.7% were still taking ibrutinib. Most patients started taking ibrutinib after 2014 (20.8% in 2014, 44.8% in 2015 and 18.8% in 2016). Patients reported fewer side effects with ibrutinib compared with other treatments. Nearly 20% (19/99) reported no side effects and, when rating acceptability of side effects, 65.9% of patients rated that the side effects of ibrutinib are non-existent or entirely acceptable. Of the 99 patients providing input, 75.8% indicated that ibrutinib improved their quality of life and brought the majority of symptoms under control.

pERC deliberated upon the rich information provided by patient groups and considered alignment of ibrutinib with patient values. pERC struggled to determine the comparative effect of ibrutinib (compared to available treatment options) on these patient values. pERC weighed the clinical trial evidence and the information provided through patient input and had difficulty with reconciling individual patient experience with clinical trial evidence that would provide data on all the experiences that patients have on treatment. Consideration was given to whether patients reporting their experiences as part of the input may have comprised a self-selected population well-enough and/or able to provide input. Additionally, pERC discussed quality-of-life data from Arm C of the PCYC-1127 trial, which indicated no change in quality of life compared with the improved quality of life reported in the patient input. Throughout its deliberations, pERC stressed the importance of robust clinical trial evidence to contextualize patient experiences and was unable to reconcile differences between the patient input and evidence reported from the trial in terms of quality of life. Although it would have been feasible to conduct randomized studies, pERC was disappointed that comparative evidence was not available so that

they could fully understand the impact of ibrutinib on outcomes important to patients. The Committee had a robust discussion on the alignment of ibrutinib with patient values, and various opinions were expressed throughout the meeting. While pERC was unable to draw a conclusion on the comparative effect of ibrutinib (with available treatment options) on patient values, pERC acknowledged that ibrutinib's ability to control disease symptoms, bring about improvements in quality of life, and provide ease of administration all aligned with patient values, based on the high quality patient input from Patient Advocacy Groups and the activity of ibrutinib. However, the Committee was unable to conclude that ibrutinib offers a net clinical benefit compared to appropriate comparators.

ECONOMIC EVALUATION

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

The pCODR Economic Guidance Panel (EGP) assessed cost-effectiveness and cost-utility analyses comparing ibrutinib with a standard care treatment mix in patients with WM who had received at least one prior therapy.

Basis of the economic model: Single-arm trial, patient chart review with imputations

Costs considered in the analysis included costs related to the drug, administration, subsequent treatment, follow-up, AE management, and terminal care.

The clinical effect considered in the analysis was based on projected OS, PFS, and health state utilities. Key clinical effect estimates for ibrutinib were based on a single-arm clinical trial (PCYC-1118E) and, for the time period following the trial follow-up, an age-adjusted mortality rate taken from the general population of Ontario. For the comparator arm, a European patient chart review was used. pERC acknowledged limitations in the use of this data source; however, in the absence of direct or indirect evidence, pERC considered the use of a chart review to be reasonable. pERC also noted that the clinical effect estimates relied heavily on extrapolation, given that the trial follow-up period was short.

Drug costs: High cost of drug

Ibrutinib costs $90.65 per 140 mg capsule. At the recommended dose of 420 mg once daily, ibrutinib costs $271.95 per day or $7614.60 per 28-day course. As provided in the submitted economic evaluation, based on a weighted average, the annual drug cost for the mix of standard of care treatments is $32,411. This would represent a per day cost of $89.04 and $2493.15 per 28-day course.

Cost-effectiveness estimates: Long term mortality risk

pERC discussed the submitted estimates and EGP's critique of the submitted incremental cost effectiveness ratio (ICER) of ibrutinib compared with a mix of standard care treatments and discussed the EGP's concerns regarding the provided model and inputs, as well as the EGP's resultant inability to provide reanalysis estimates. pERC noted that limitations in the available non-randomized clinical evidence for ibrutinib and the absence of long-term data on the survival benefit gained with ibrutinib in this setting contributed greatly to this uncertainty. pERC discussed the assumption made in the base-case results that model patients who receive ibrutinib as having the same mortality risk as the general population (adjusting for age). In the absence of evidence to suggest ibrutinib provides such a survival advantage, pERC agreed that this approach is inappropriate. The Committee acknowledged that without an alternative data source, the mortality risk for patients on ibrutinib is unquantifiable. Therefore, pERC appreciated and acknowledged the one-way sensitivity analyses performed by the EGP to adjust mortality risk of the ibrutinib arm to 10%, 25%, 50%, and 75% of that of the standard of care group as a means to illustrate the impact that changes in the relative mortality of ibrutinib compared with a standard care mix would have on the ICER. pERC agreed that this limitation created the largest uncertainty in the ICER. pERC also agreed that, based on the age and disease course of patients, it would not be appropriate to model a 20 year time horizon as done in the base case. Specifically, pERC agreed with the EGP that a five year time horizon would be more appropriate. In a one way sensitivity analysis exploring a five year time horizon alone, the ICER more than doubled from the base case results. Finally, pERC agreed with the EGP's reduction of utility values by 10% to better reflect the poor prognosis in this population. In the absence of an estimate to quantify the ICER, pERC agreed that it was challenging to determine the true ICER. Therefore, given the lack of robust direct or indirect evidence comparing ibrutinib with appropriate comparators and uncertainty in the long term benefit conferred with ibrutinib, pERC agreed that ibrutinib could not be considered cost-effective. pERC further acknowledged that the treatment mix used in the

base case analysis contained a large number of expensive rituximab based regimens. In a scenario where ibrutinib may be used in a rituximab refractory population, pERC noted that the incremental cost of ibrutinib would be higher as the cost of available standard treatments would be less when rituximab is removed from the mix

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: High drug cost, lack of long-term comparative data, oral therapy

pERC discussed factors affecting the feasibility of implementing a reimbursement recommendation for ibrutinib for patients with previously treated WM. pERC acknowledged the PAG's concerns over the lack of long-term comparative evidence. pERC stressed this concern throughout its deliberations and concluded that there was no net clinical benefit with the use of ibrutinib compared to available treatment options. In addition, pERC agreed that this created considerable uncertainty regarding the cost effectiveness estimates. While acknowledging the small number of patients with WM relative to other cancers, pERC agreed that a randomized study would have been feasible in this setting.

pERC noted that there was no evidence available on the efficacy and safety of ibrutinib plus rituximab combination therapy. Arms A and B of the randomized portion of study PCYC-1127 are expected to provide data on this combination treatment both in the newly diagnosed and previously treated setting. pERC further acknowledged that the current evidence, from small non- randomized studies, was not sufficient to conclude that there was a net clinical benefit with ibrutinib in the previously treated setting. pERC agreed that ibrutinib's oral route of administration creates ease of administration for patients and is an enabler to implementation, yet the differential mechanisms for funding oral medications (i.e. not the same as IV cancer medications) in some jurisdictions may also be a barrier to implementation. This differential mechanism of funding would place financial and practical limitations on patients and caregivers. Furthermore, the drug's high cost is a barrier to implementation. While adverse events associated with ibrutinib were considered to be manageable, pERC agreed that health care professionals will need to become familiar with monitoring and managing the drug-drug interactions associated with ibrutinib, especially since it is metabolized in the liver by the CYP3A and cytochrome P450.

DRUG AND CONDITION INFORMATION

Drug Information	• Selective Bruton's tyrosine kinase (BTK) inhibitor • 140 mg capsule size • Recommended dosage of 420 mg administered orally, once daily
Cancer Treated	• Waldenström's Macroglobulinemia
Burden of Illness	• Uncommon disease with an incidence of 3-5 per million in the US • Median survival is 5 years • Need for benefit over available treatment options in terms of symptom control, improvement in quality of life and longer remission rates are a continued need for patients.
Current Standard Treatment	• No standard treatment available however various single agents and combination regimens are available and used
Limitations of Current Therapy	• No standard treatment option

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

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

- Jo Nanson, who did not vote due to her role as a patient member alternate
- Matthew Cheung 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 ibrutinib (Imbruvica) for waldenström's macroglobulinemia, through their declarations, six 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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