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Reimbursement Recommendation

Acalabrutinib (Calquence)

Indication: For the treatment of patients with previously untreated chronic lymphocytic leukemia

Sponsor: AstraZeneca Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Calquence in Combination With Venetoclax?

Canada's Drug Agency (CDA-AMC) recommends that Calquence in combination with venetoclax be reimbursed by public drug plans for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) if certain conditions are met.

Why Did CDA-AMC Recommend Reimbursement?

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) determined that Calquence in combination with venetoclax demonstrates acceptable clinical value compared with chemoimmunotherapy (fludarabine-cyclophosphamide-rituximab [FCR] or bendamustine-rituximab [BR]) in patients with previously untreated CLL. Given that acalabrutinib-venetoclax is expected to be an alternative to chemoimmunotherapy, acceptable clinical value refers to added value versus chemoimmunotherapy.

Evidence from a clinical trial (the AMPLIFY trial) showed that in adult patients with previously untreated CLL, treatment with Calquence in combination with venetoclax delayed disease progression or death compared with chemoimmunotherapy (FCR or BR). The results for the other secondary outcomes — including overall response rate, duration of response, and event-free survival — further supported the findings. However, there was not enough certainty that the treatment could prolong overall survival (OS).

Which Patients Are Eligible for Coverage?

Calquence in combination with venetoclax should only be covered for the treatment of adults with previously untreated active CLL who need treatment and with good performance status. Calquence in combination with venetoclax should not be covered for patients with Richter syndrome, cancer spreading to the central nervous system, uncontrolled autoimmune hemolytic anemia, or idiopathic thrombocytopenic purpura.

What Are the Conditions for Reimbursement?

Calquence in combination with venetoclax should be prescribed by clinicians with expertise in managing CLL. Reimbursement should be discontinued if the cancer progresses, the patient has unacceptable side effects, or the full 14 cycles of treatment are completed.

Summary

The total treatment cost of Calquence plus venetoclax does not exceed the total cost of treatment with ibrutinib-venetoclax for the same indication.

Review Background

- **Disease background**: CLL is a slow-growing and incurable blood cancer that happens when the body produces too many abnormal B cells, which build up in the blood, bone marrow, lymph nodes, and spleen. In Canada, CLL accounts for about 44% of all leukemia cases, with an estimated 1,700 new cases reported in 2019.
- **Indication and reimbursement request:** Acalabrutinib (Calquence), in combination with venetoclax, has been approved by Health Canada for the treatment of patients with previously untreated CLL. The sponsor is seeking reimbursement for this patient population.
- **Drug under review:** Calquence is a second-generation, highly selective, covalent Bruton tyrosine kinase (BTK) inhibitor and the dosage recommended in the product monograph is 100 mg taken orally twice daily for a total of 13 months, until disease progression, or unacceptable toxicity. In the fixed-duration regimen with venetoclax, Calquence is administered as monotherapy for the first two 28-day cycles, followed by 12 cycles of Calquence in combination with venetoclax.
- **Treatment costs:** At the submitted price of $142.77 per tablet, the 28-day cost of Calquence is expected to be $7,995 per patient, based on the Health Canada–recommended dosage. Calquence is indicated for use in combination with venetoclax; the cost of the regimen is expected to be $9,828 per patient in cycle 3 and $15,925 per patient per cycle in subsequent cycles.

Highlights of Input From Interested Parties

The patient group (Lymphoma Canada) noted the following regarding impacts of the disease, unmet needs, and important outcomes:

- As CLL progresses, symptoms may include fatigue, anxiety, frequent infections, and limitations in daily activities.
- The negative impacts of CLL are emotional distress, loss of independence, disruption to employment and family life, and reduction in quality of life.
- Important treatment outcomes include delaying the disease from getting worse, living longer, managing disease symptoms, fewer side effects, and improved quality of life.
- There remains a need for more convenient, fixed-duration, and better-tolerated treatment options that reduce disruption to daily life.

The clinician groups (the Leukemia and Lymphoma Society of Canada Nurse Practitioners Network, Lymphoma Canada, and Ontario Health [Cancer Care Ontario] Hematology Cancer Drug Advisory Committee) and the clinical experts consulted by CDA-AMC noted the following regarding unmet needs arising from the disease and place in therapy for the drug under review:

- There is a need for a safer, fixed-duration, all-oral regimen that provides sustained remission, eliminates the need for IV administration, enhances treatment adherence, and reduces the risk of discontinuation due to adverse events (AEs).

- Calquence in combination with venetoclax is anticipated to serve as an alternative first-line combination regimen for the treatment of previously untreated CLL.

The participating public drug programs raised potential implementation issues related to relevant comparators, considerations for initiation, discontinuation, and prescribing of therapy; generalizability of trial populations to broader populations; and potential need for a Provisional Funding Algorithm.

Recommendation

With a vote of 14 in favour to 0 against, pERC recommends that acalabrutinib in combination with venetoclax (acalabrutinib-venetoclax) be reimbursed for the treatment of patients with previously untreated CLL only if the conditions listed in Table 1 are met.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with acalabrutinib-venetoclax should be reimbursed in adults with previously untreated CLL and active disease that requires treatment per IWCLL 2018 criteria.[a]	Evidence from the AMPLIFY trial showed that treatment with acalabrutinib-venetoclax compared with investigator's choice of chemoimmunotherapy (FCR or BR) resulted in clinical benefit in patients with these characteristics.	—
2. Patients should have a good performance status.	Patients with an ECOG PS score of 0 to 2 were included in the AMPLIFY trial.	—
3. Patients must not have any of the following: 3.1. Richter syndrome 3.2. CNS involvement 3.3. uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura.	No evidence was identified to demonstrate a benefit of acalabrutinib-venetoclax in patients with Richter syndrome, CNS involvement, uncontrolled autoimmune hemolytic anemia, or thrombocytopenia, as these patients were not enrolled in the AMPLIFY trial.	Patients with del(17p) and/or *TP53* mutations were excluded from the AMPLIFY trial. pERC agreed with clinical experts that treatment with acalabrutinib-venetoclax would be a reasonable option, at the discretion of the treating clinician, for patients with detected del(17p) and/or *TP53* mutation. Patients with SLL were excluded from the AMPLIFY trial. pERC agreed with the clinical experts that it would be reasonable to generalize the AMPLIFY trial results to patients with SLL.
Discontinuation		
4. Treatment with acalabrutinib-venetoclax should be discontinued upon the occurrence of any of the following: 4.1. disease progression 4.2. unacceptable toxicity	In the AMPLIFY trial, acalabrutinib was administered as a single drug for 2 cycles (each cycle is 28 days), followed by 12 cycles of acalabrutinib-venetoclax. Patients in the AMPLIFY trial discontinued treatment if they experienced disease progression or unacceptable toxicity.	Evidence to support re-treatment with acalabrutinib-venetoclax upon progression was not available at the time of this review. However, pERC agreed with the clinical experts that re-treatment at the discretion of the treating clinician may be considered for patients who experience progression and have had at least 1 year of response

Reimbursement condition	Reason	Implementation guidance
4.3. completion of 14 cycles of therapy.		following completion of the initial course of acalabrutinib-venetoclax. Similarly, pERC agreed with clinical experts that a comparable approach would be reasonable for patients who experience disease progression during a treatment break. In such cases, re-treatment with acalabrutinib-venetoclax may be considered at the discretion of the treating clinician, provided that at least 1 year has elapsed from the start of the treatment break. The clinical experts indicated that this approach is consistent with current practices for venetoclax-obinutuzumab and ibrutinib-venetoclax, where similar re-treatment strategies are applied.
Prescribing		
5. Acalabrutinib-venetoclax should be prescribed by clinicians with expertise in managing CLL.	This will ensure that acalabrutinib-venetoclax is prescribed for appropriate patients and that adverse effects are managed in an optimal and timely manner.	pERC agreed with clinical experts that, in cases where a patient discontinues acalabrutinib early due to intolerance (e.g., severe hypertension) but has no evidence of disease progression, it would be appropriate to continue venetoclax for the remainder of the planned treatment duration. In the AMPLIFY trial, patients were allowed to continue receiving the remaining study drug if 1 component of the regimen was permanently discontinued due to intolerance or toxicity. Specifically, if acalabrutinib was discontinued, venetoclax could be continued, and vice versa.
Pricing		
6. The total treatment cost of acalabrutinib-venetoclax should be negotiated so that it does not exceed the total cost of treatment with ibrutinib-venetoclax for the same indication.	Based on the committee's assessment of the evidence, acalabrutinib-venetoclax is expected to have comparable health outcomes compared with relevant comparators. Therefore, the total treatment cost of acalabrutinib-venetoclax should be no more than ibrutinib-venetoclax.	—

BR = bendamustine-rituximab; CLL = chronic lymphocytic leukemia; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FCR = fludarabine-cyclophosphamide-rituximab; IWCLL = International Workshop on Chronic Lymphocytic Leukemia; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; SLL = small lymphocytic leukemia.

[a]Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-2760. doi: https://doi.org/10.1182/blood-2017-09-806398.

Rationale for the Recommendation

Clinical Value

Based on the totality of the clinical evidence, pERC concluded that acalabrutinib-venetoclax demonstrates acceptable clinical value compared with chemoimmunotherapy of investigator's choice (FCR or BR) in patients with previously untreated CLL. Given that acalabrutinib-venetoclax is expected to be an alternative to chemoimmunotherapy, acceptable clinical value refers to added value versus chemoimmunotherapy.

Evidence from the phase III AMPLIFY trial demonstrated that treatment with acalabrutinib-venetoclax likely results in added clinical benefit in progression-free survival (PFS) in adults with previously untreated CLL. Treatment with acalabrutinib-venetoclax was associated with statistically significant and clinically meaningful improvements in PFS compared with investigator's choice of chemoimmunotherapy (FCR or BR) (primary analysis: median PFS = not reached versus 47.6 months; hazard ratio = 0.65; 95% confidence interval [CI], 0.49 to 0.87). At a median follow-up time of approximately 41 months, the 48-month between-group difference in PFS rates was 15.2% (95% CI, [redacted]). The outcomes of other secondary end points – including overall response rate, duration of response, and event-free survival – further supported the findings of the primary analysis. pERC noted that the AMPLIFY trial was not powered to detect differences in OS and only 10% of the expected events had occurred at the interim analysis ([OS hazard ratio = 0.33; 95% CI, 0.18 to 0.56] the 48-months between-group difference in OS rates was 12.7%; 95% CI, [redacted]). pERC considered clinician input indicating that the safety profile of acalabrutinib-venetoclax observed in the AMPLIFY trial appeared consistent with the established safety profiles of the individual drugs in the regimen, which are regarded as generally predictable and manageable.

There was no evidence comparing acalabrutinib-venetoclax with acalabrutinib, zanubrutinib, or ibrutinib monotherapy; venetoclax-obinutuzumab; or ibrutinib-venetoclax, which were identified as relevant comparators for patients with previously untreated CLL. Therefore, the comparative efficacy and safety of acalabrutinib-venetoclax versus these alternative treatments remain unknown.

Patients and clinicians identified the need for effective treatment options that delay disease progression, extend survival, improve disease and symptom control, minimize side effects, improve quality of life, and provide convenient administration and additional treatment choice. pERC concluded that, compared to chemoimmunotherapy, acalabrutinib-venetoclax met some of the identified needs as it likely delays disease progression, has manageable side effects, and offers an additional treatment option with a convenient oral route of administration and a fixed treatment duration. The impact of acalabrutinib-venetoclax on health-related quality of life (HRQoL) compared to chemoimmunotherapy was very uncertain due to the open-label design of the trial and the large amount of missing data.

Further information on the committee's discussion around clinical value is provided in the Summary of Deliberation section.

Developing the Recommendation

The determination of acceptable clinical value was sufficient for pERC to recommend reimbursement of acalabrutinib-venetoclax. As part of the deliberation on whether to recommend reimbursement, the committee also considered unmet clinical need, unmet nonclinical need, and health inequity. Information on this discussion is provided in the Unmet Clinical Need and Distinct Social and Ethical Considerations subsections in the Summary of Deliberation section.

Because pERC recommended that acalabrutinib-venetoclax be reimbursed, the committee also deliberated on whether reimbursement conditions should be added to address important economic considerations, health system impacts, or social and ethical considerations, or to ensure clinical value is realized. The resulting reimbursement conditions, with accompanying reasons and implementation guidance, are stated in Table 1.

Summary of Deliberation

pERC considered all domains of value of the deliberative framework before developing its recommendation: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems. For further information on the domains of value, refer to Expert Committee Deliberation at CDA-AMC.

The committee considered the following key discussion points, organized by the 5 domains of value.

Clinical Value

- **Appropriate comparators**: According to the clinical experts, chemoimmunotherapy has largely been replaced by continuous BTK inhibitor monotherapy (ibrutinib, acalabrutinib, or zanubrutinib) or targeted fixed-duration combinations (venetoclax-obinutuzumab or ibrutinib-venetoclax) to treat patients with previously untreated CLL. pERC heard from the clinical experts that chemoimmunotherapy was commonly used when the AMPLIFY trial was initiated and was the control arm of several pivotal trials in the first-line CLL setting. Of note, ibrutinib-venetoclax and venetoclax-obinutuzumab received conditional positive final CDA-AMC recommendations, informed by the GLOW and GAIA phase III trials, respectively, comparing these regimens against immunochemotherapies (GLOW: versus chlorambucil-obinutuzumab; GAIA: versus FCR or BR). In the absence of direct or indirect comparative evidence, pERC discussed that the efficacy and safety of acalabrutinib-venetoclax compared to acalabrutinib, zanubrutinib, or ibrutinib monotherapy; venetoclax-obinutuzumab; or ibrutinib-venetoclax, remains unknown.
- **Efficacy versus chemoimmunotherapy of investigator's choice:** One phase III, open-label, randomized controlled trial (AMPLIFY) demonstrated that treatment with acalabrutinib-venetoclax was associated with statistically significant improvements in PFS compared with chemoimmunotherapy of investigator's choice. However, pERC noted that the AMPLIFY trial was not powered to demonstrate

a difference in OS, the interim analysis was based on a small information fraction (10% [60 of 520] of the expected OS events), and the duration of follow-up was insufficient to capture long-term OS benefit. Given these limitations, pERC could not draw definitive conclusions on the comparative OS results from the AMPLIFY trial.

- **Clinical importance of treatment effects**: pERC discussed the clinical meaningfulness of PFS in previously untreated CLL and agreed with clinical experts that improvements in PFS have not been shown to reliably predict improvements in OS in this population. However, pERC agreed with input provided by clinician groups and clinical experts that delaying disease progression is a meaningful outcome for patients as CLL remains incurable and most patients will ultimately experience disease progression. Moreover, PFS is an established clinical end point in pivotal clinical trials for the target patient population. pERC concurred with clinical experts that an absolute difference of at least 10% in PFS rates at 48 months represents a clinically meaningful benefit in the current therapeutic setting.
- **Generalizability:** pERC discussed the use of acalabrutinib-venetoclax in patients with a del(17p) and/or *TP53* mutation. These patients were excluded from the AMPLIFY trial because of inferior response to chemoimmunotherapy treatment. However, given clinical experience of related drug regimens, including venetoclax, in patients with CLL who have the del(17p) and/or *TP53* mutations, pERC agreed with the clinical experts that it may be appropriate to consider treatment with acalabrutinib-venetoclax in these patients. In consultation with the clinical experts consulted for this submission, pERC noted that it is important to consider the toxicity profile of acalabrutinib-venetoclax compared to other options when making this treatment decision. pERC discussed the use of acalabrutinib-venetoclax in patients with small lymphocytic lymphoma (SLL). These patients were excluded from the AMPLIFY trial. pERC heard from the clinical experts that the pathologic and immunophenotypic features of the malignant cells are identical in CLL and SLL and both are treated similarly in clinical practice in Canada. pERC agreed with the clinical experts that it would be reasonable to generalize the AMPLIFY trial results to patients with SLL, as SLL and CLL represent different manifestations of the same underlying disease.
- **Harms results:** Comparative safety from the AMPLIFY trial indicated that the occurrence of treatment emergent AEs of any grade, serious adverse events (SAEs), and treatment discontinuations due to AEs was similar across treatment groups. Headache, diarrhea, alopecia, COVID-19, and contusion were the most common treatment emergent AEs in the acalabrutinib-venetoclax group and occurred more frequently in this group relative to chemoimmunotherapy. There were less patients experiencing grade 3 or greater AEs in the acalabrutinib-venetoclax group than in the chemoimmunotherapy group. pERC heard from the clinical experts that the safety profile of the combination of acalabrutinib-venetoclax was consistent with the known profiles of the individual drugs and no new safety signals were observed in the AMPLIFY trial. Overall, pERC agreed with the clinical experts that the adverse effects associated with acalabrutinib-venetoclax appeared generally predictable and manageable.
- **Certainty of the evidence**: The assessment of PFS at 48 months was rated as “moderate” certainty of evidence based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment. There is “low” level of certainty that acalabrutinib-venetoclax may result in

a clinically meaningful increase in the probability of being alive at 48 months when compared with chemoimmunotherapy based on the 5% threshold suggested by the clinical experts consulted by CDA-AMC. As noted, the AMPLIFY trial was not powered to demonstrate a difference in OS. The assessment of HRQoL (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Global Health Status score) was rated as "low" to "very low" certainty of evidence due to very serious risk of bias (missing data and bias due to the open-label study design). Results for SAEs were associated with "low" certainty of evidence, suggesting that acalabrutinib-venetoclax may result in a decrease in SAEs.

- **Clinical value:** Based on the preceding considerations, pERC determined there was added clinical value versus chemoimmunotherapy.

Unmet Clinical Need

- **Input on unmet clinical need**: Patients identified a need for new treatments for CLL that prolong survival and remission, have fewer side effects, and improve HRQoL. The submitted patient group input indicated that despite the availability of effective therapies, patients highlighted ongoing unmet needs, including the burden of long treatment durations, and treatment-related toxicities. The clinical experts consulted for this review and input received from clinician groups highlighted the need for a safer regimen that offers prolonged remission, reduces the cardiac risks associated with continued BTK inhibitors (especially ibrutinib), and lowers the risk of treatment discontinuation due to AEs.
- **Severity of the disease**: CLL is the most common leukemia in adults. Treatment is typically initiated when there is evidence of disease progression or the development of symptoms indicating active disease, and most patients ultimately require therapy during the course of their illness. CLL remains an incurable condition, with an estimated 5-year net survival rate of about 83%. The primary aims of treatment are to extend survival and enhance quality of life. The clinical experts further noted that certain high-risk molecular or genetic subgroups with CLL experience poor outcomes, particularly with conventional chemoimmunotherapies.
- **Availability of treatment options**: Available targeted therapies include chemoimmunotherapy (e.g., FCR or BR), BTK inhibitors (e.g., ibrutinib, acalabrutinib, and zanubrutinib), a B-cell lymphoma 2 inhibitor (e.g., venetoclax), and next-generation anti-CD20 monoclonal antibodies (e.g., obinutuzumab). Chemoimmunotherapy regimens are administered intravenously and have been largely replaced by continuous BTK inhibitor monotherapy (ibrutinib, acalabrutinib, or zanubrutinib) or targeted fixed-duration combinations (venetoclax-obinutuzumab or ibrutinib-venetoclax) to treat patients with previously untreated CLL. According to the clinical experts consulted by CDA-AMC chemoimmunotherapy is rarely used, reserved only for select younger active patients with favourable molecular features (*IGHV* mutated). According to the clinical experts consulted by CDA-AMC and input from clinician groups, venetoclax-obinutuzumab requires IV administration and carries a risk of tumour lysis syndrome due to venetoclax, necessitating close monitoring during treatment initiation. Further, the experts noted that ibrutinib-venetoclax combinations raise safety concerns, especially due to ibrutinib-associated cardiovascular toxicity in older patients with comorbidities.

Distinct Social and Ethical Considerations

- **Input on unmet nonclinical need:** Patients and clinicians identified the need for effective treatment options that provide convenient administration and reduce logistical challenges such as travel and associated costs, especially for patients residing in rural or remote areas. pERC noted that oral medications can generally be taken at home, potentially reducing the logistical burden associated with therapies that require IV administration in an infusion centre. However, pERC noted that in some jurisdictions, oral medications are not funded through the same mechanism as IV cancer therapies. As a result, patients may face additional access challenges to oral treatments.

  The clinical experts consulted for this review and input received from clinician groups highlighted the need for a fixed-duration regimen that reduces the burden of long treatment durations and treatment-related toxicities along with improved adherence. pERC heard from the clinical experts consulted by CDA-AMC that a fixed-duration regimen, such as acalabrutinib-venetoclax, may be preferred by some patients compared with the continuous, indefinite administration required with BTK inhibitor monotherapy.

  pERC deliberated on safety concerns with currently available therapies. The committee discussed that reducing reliance on therapies with known safety risks (e.g., ibrutinib-associated cardiovascular toxicity) may be particularly important for patients with pre-existing cardiovascular conditions or for those who are older and more susceptible to treatment-related AEs. pERC agreed with the clinical experts consulted by CDA-AMC that acalabrutinib-venetoclax may potentially address these concerns by offering a regimen that avoids prolonged exposure to therapies associated with higher rates of cardiovascular toxicity.
- **Ethical implications:** pERC discussed the potential challenges associated with managing treatment with acalabrutinib-venetoclax, noting that the initiation of venetoclax requires careful monitoring for tumour lysis syndrome, including multiple weekly blood extraction and supportive care. For patients in rural or remote areas, limited access to cancer centres creates significant logistical and emotional challenges, disrupting daily life.

Economic Considerations

- **Health impacts of acalabrutinib-venetoclax versus relevant comparators:** Due to the lack of direct or indirect evidence, no definite conclusion can be drawn on the comparable efficacy of acalabrutinib-venetoclax against nonchemoimmunotherapy comparators (i.e., ibrutinib-venetoclax; venetoclax-obinutuzumab; and acalabrutinib, ibrutinib, and zanubrutinib monotherapy) for patients with previously untreated CLL. Conclusions about the comparative harms and impact on HRQoL, which were deemed important by patient and clinician groups, could not be made as these outcomes were also not assessed. The predicted health impact of acalabrutinib-venetoclax versus FCR or BR in the economic model was uncertain due to limitations with the submitted cost-utility analysis.
- **Cost of acalabrutinib-venetoclax versus relevant comparators:** If it is anticipated that there are no differences in health outcomes between acalabrutinib-venetoclax versus

nonchemoimmunotherapy comparators, then the impact of acalabrutinib-venetoclax on costs will be most dependent on the drug acquisition costs. The incremental cost of acalabrutinib-venetoclax versus ibrutinib-venetoclax and venetoclax-obinutuzumab is dependent on the regimen duration such that if treatment with acalabrutinib-venetoclax is longer than the comparator the incremental cost will increase. The cost of acalabrutinib-venetoclax was lower than BTK inhibitor monotherapy due to shorter treatment duration (14 cycles versus treat to progression).

  - The health system cost of acalabrutinib-venetoclax versus FCR or BR is uncertain due to limitations with the sponsor's analysis including the overestimation of postprogression benefit.

- **Key findings of the economic evaluation:** Based on evidence reviewed for this submission, there is no robust evidence to suggest that acalabrutinib-venetoclax provides greater health benefit than any of the relevant comparators. If it is anticipated that there are no differences in health outcomes between acalabrutinib-venetoclax versus ibrutinib-venetoclax, venetoclax-obinutuzumab, and BTK inhibitor monotherapies, then the cost of acalabrutinib-venetoclax should not exceed that of those comparators for the treatment of adult patients with previously untreated CLL.
  - The cost-effectiveness of acalabrutinib-venetoclax versus FCR or BR is highly uncertain due to the limitation in the economic analysis. Based on clinical expert feedback and data presented by the sponsor, the use of FCR or BR for this indication is anticipated to be small (around 1%) and is unlikely to be impacted should acalabrutinib-venetoclax become available. Therefore, FCR or BR may not be considered a relevant comparator and the cost-effectiveness versus this comparator is likely not relevant for decision-makers.
- **Certainty of the evidence:** No indirect treatment comparison was submitted by the sponsor for this review based on the lack of feasibility of conducting a robust comparison. As a result, there is currently no direct or indirect evidence to assess the relative efficacy and safety of acalabrutinib-venetoclax against ibrutinib-venetoclax; venetoclax-obinutuzumab; and acalabrutinib, ibrutinib, and zanubrutinib monotherapy. The pERC deliberation found it reasonable to consider them comparable in efficacy. Additionally, the limitations with the sponsor's model structure introduced additional uncertainty in the predicted benefit of acalabrutinib-venetoclax compared to FCR or BR.
- **Other considerations:** Patients with del(17p) or *TP53* mutations were excluded from the AMPLIFY trial due to ethical concerns regarding the poor efficacy of the chemoimmunotherapy comparators in this patient population at the time that the trial was conducted. Clinical expert feedback suggested that these patients may still benefit from acalabrutinib-venetoclax in clinical practice. However, the cost-effectiveness of acalabrutinib-venetoclax in individuals with del(17p) and *TP53* mutations is unknown.

Impacts on Health Systems

- **Anticipated budget impact:** It is estimated that 2,493 patients who were diagnosed would be eligible for treatment with acalabrutinib-venetoclax over a 3-year period (year 1 = 762; year 2 = 833; year 3 = 897), of whom [redacted] are expected to receive acalabrutinib-venetoclax (year 1 = [redacted]; year

2 = [redacted]; year 3 = [redacted]). The estimated budget impact of reimbursing acalabrutinib-venetoclax is predicted to be approximately $29 million for the combined incident and prevalent populations for the first 3 years, with an expected expenditure of $87 million on acalabrutinib and estimated expenditure on acalabrutinib-venetoclax of $155 million. The estimated budget impact will depend on the uptake of acalabrutinib-venetoclax and time to treatment discontinuation of BTK inhibitor monotherapies.

Sources of Information Used by the Committee

To make its recommendation, the committee and subcommittee considered the following information (links to the full documents for the review can be found on the project webpage):

- the review by CDA-AMC of the clinical and pharmacoeconomic evidence submitted by the sponsor, as well as relevant ethical issues related to acalabrutinib-venetoclax (refer to the Supplemental Material document)
- the sponsor's comments on the draft report and the responses by CDA-AMC
- patients' perspectives gathered by 1 patient group, Lymphoma Canada (refer to the Patient and Clinician Group Input document)
- input from 3 clinician groups, the Leukemia and Lymphoma Society of Canada Nurse Practitioners Network, Lymphoma Canada, and the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee (refer to the Patient and Clinician Group Input document)
- input from public drug programs that participate in the reimbursement review process (refer to the Supplemental Material document)
- input from 2 clinical experts with expertise in the management of CLL consulted by CDA-AMC.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Kelvin Chan (Vice-Chair), Paul Agbulu, Dr. Phillip Blanchette, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Michael Raphael, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: November 12, 2025

Regrets: Four expert committee members did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca