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## Reimbursement Recommendation

# Venetoclax (Venclexta)

**Indication:** In combination with ibrutinib, for the treatment of adult patients with relapsed or refractory mantle cell lymphoma

**Sponsor:** AbbVie Corporation

**Final recommendation:** Reimburse with conditions

# Summary

## What Is the Reimbursement Recommendation for Venclexta?

Canada's Drug Agency (CDA-AMC) recommends that Venclexta, in combination with ibrutinib (Venclexta plus ibrutinib), be reimbursed by public drug plans for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Venclexta should only be covered for adults who are in relatively good health and have already tried at least 1 other treatment for this disease.

### What Are the Conditions for Reimbursement?

Venclexta should only be reimbursed if it is prescribed by clinicians with expertise in managing MCL and monitoring therapy, and the cost of Venclexta is reduced.

### Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Venclexta plus ibrutinib may delay disease progression and prolong life in patients with relapsed or refractory MCL.
- Venclexta meets some patient needs as it is an alternative treatment option that may offer benefits in disease control.
- Based on the CDA-AMC assessment of the health economic evidence, Venclexta does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Venclexta plus ibrutinib is estimated to cost the public drug plans approximately $43 million over the next 3 years.

## Additional Information

### What Is MCL?

MCL is a frequently aggressive subtype of B-cell non-Hodgkin lymphoma (NHL). MCL accounts for approximately 5% to 7% of NHL cases. It was estimated that 11,700 people in Canada were diagnosed with NHL in 2024.

### Unmet Needs in Relapsed or Refractory MCL

Patients with relapsed or refractory MCL have an unmet need for effective treatment options that can prolong life, achieve longer disease remission, improve quality of life, and have fewer side effects.

# Summary

**How Much Does Venclexta Cost?**

Treatment with Venclexta is expected to cost approximately $7,930 per patient per 28-day cycle (Venclexta plus ibrutinib = $19,111 per cycle).

## Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that venetoclax in combination with ibrutinib (venetoclax plus ibrutinib) be reimbursed for the treatment of adult patients with relapsed or refractory MCL only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

Evidence from the randomized phase of the SYMPATICO study, which was a phase III, multicentre, double-blind randomized controlled trial (RCT) (N = 267), demonstrated that treatment with venetoclax plus ibrutinib may result in an added clinical benefit, compared to treatment with placebo plus ibrutinib, for patients with MCL who have received at least 1, but no more than 5, prior treatment regimens for MCL, including at least 1 prior rituximab- or anti-CD20 antibody–containing regimen. With a median time on study of [redacted] ([redacted]) for the venetoclax plus ibrutinib group and [redacted] ([redacted]) for the placebo plus ibrutinib group, the median progression-free survival (PFS) per investigator assessment (primary end point) was 31.9 months (95% confidence interval [CI], 22.8 to 47.0) in the venetoclax plus ibrutinib group and 22.1 months (95% CI, 16.5 to 29.5) in the placebo plus ibrutinib group. The hazard ratio (HR) for progression per investigator assessment was 0.645 (95% CI, 0.474 to 0.878). The difference in the probability of being progression free between the venetoclax plus ibrutinib group and the placebo plus ibrutinib group was [redacted] (95% CI, [redacted] to [redacted]) at 36 months and [redacted] ([redacted]) at 60 months. In the interim analysis of overall survival (OS), the median OS was 44.9 months (95% CI, 31.9 to not estimable) in the venetoclax plus ibrutinib group and 38.6 months (95% CI, 25.2 to 53.4) in the placebo plus ibrutinib group. The HR for death was 0.854 (95% CI, 0.615 to 1.186). The difference in the probability of being alive between the venetoclax plus ibrutinib group and the placebo plus ibrutinib group was [redacted] (95% CI, [redacted] to [redacted]) at 48 months and [redacted] (95% CI, [redacted] to [redacted]) at 60 months.

Patients identified a need for new effective treatment options that prolong life, achieve longer disease remission, control disease symptoms, improve quality of life, and have fewer side effects. pERC concluded that venetoclax plus ibrutinib met some patients' needs, notably improving PFS. Patients treated with venetoclax plus ibrutinib experienced more side effects than those associated with ibrutinib alone. However, pERC noted that given the potential for improved efficacy (PFS), some patients may still opt for venetoclax plus ibrutinib despite the increased risk of toxicities associated with the treatment.

Using the sponsor-submitted price for venetoclax and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for venetoclax plus ibrutinib was $360,148 per quality-adjusted life-year (QALY) gained compared with ibrutinib monotherapy. At this ICER, venetoclax plus ibrutinib is not cost-effective at a $50,000 per QALY willingness to pay threshold for patients with MCL who have received at least 1 prior line of therapy. A price reduction is required for venetoclax plus ibrutinib to be considered cost-effective at a $50,000 per QALY threshold.

## Table 1: Reimbursement Conditions and Reasons

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Initiation** | | |
| 1. Treatment with venetoclax plus ibrutinib should be initiated in patients with MCL who meet all the following criteria:<br>1.1. 18 years of age or older<br>1.2. have received at least 1 prior line of therapy for MCL<br>1.3. have good performance status. | In the randomized phase of the SYMPATICO study, venetoclax plus ibrutinib demonstrated an added clinical benefit, compared to placebo plus ibrutinib, in patients (≥ 18 years) with pathologically confirmed MCL who had received 1 to 5 prior therapies (including at least 1 prior rituximab- or anti-CD20–containing regimen), had disease that had failed to achieve at least partial response with or documented progression after the most recent treatment regimen, and had an ECOG PS of 0 to 2. | Based on clinical expert input, pERC noted that selected patients with an ECOG PS greater than 2 may be eligible for treatment with venetoclax plus ibrutinib.<br>pERC agreed with the clinical experts that it would be reasonable to initiate (re-treat with) venetoclax plus ibrutinib in patients who have received prior treatment containing a BTK or BCL2 inhibitor if they had no evidence of progressive disease during the treatment and treatment concluded at least 6 months prior (e.g., if the disease recurs during an ibrutinib monotherapy break or at least 6 months after achieving good response to venetoclax plus ibrutinib and stopping treatment). |
| **Discontinuation** | | |
| 2. The maximum treatment duration of venetoclax should not exceed 24 months. | In the randomized phase of the SYMPATICO study, venetoclax was administered for a maximum of 24 months. | — |
| 3. Treatment with venetoclax plus ibrutinib should be discontinued on the occurrence of any of the following:<br>3.1. disease progression<br>3.2. unacceptable toxicity. | In the randomized phase of the SYMPATICO study, treatment with venetoclax plus ibrutinib was continued until disease progression, unacceptable toxicity, patient withdrawal, or death. | — |
| 4. If 1 component of venetoclax plus ibrutinib is discontinued permanently because of tolerability concerns, the patient may continue to receive the other component at the discretion of the treating physician, until the discontinuation criteria in condition 2 or condition 3 are met. | This condition reflects the treatment discontinuation criteria in the randomized phase of the SYMPATICO study. | In the absence of evidence, pERC could not recommend using an alternative BTK inhibitor with venetoclax in patients who have intolerance to ibrutinib. |
| **Prescribing** | | |
| 5. Venetoclax plus ibrutinib should be prescribed by clinicians with expertise in managing MCL and monitoring therapy. | This condition is meant to ensure that venetoclax plus ibrutinib is prescribed only for appropriate patients and that adverse effects are managed in an optimized and timely manner. | — |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Pricing** | | |
| 6. A reduction in price. | The ICER for venetoclax plus ibrutinib is $360,148 when compared with ibrutinib monotherapy.<br>Price reductions greater than 90% for venetoclax will be required for venetoclax plus ibrutinib to achieve an ICER of $50,000 per QALY gained compared to ibrutinib monotherapy. Price reductions for different thresholds are available in Appendix 4 in the Pharmacoeconomic Review report. | — |

BTK = Bruton tyrosine kinase; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost=-effectiveness ratio; MCL = mantle cell lymphoma; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year.

## Discussion Points

- **Unmet needs**: Aligned with the input from the patient group and clinicians, pERC acknowledges that there is an unmet need for effective treatment options for patients with relapsed or refractory MCL. Based on the currently available evidence from the randomized phase of the SYMPATICO study, pERC concluded that venetoclax plus ibrutinib may meet some of the unmet needs by delaying disease progression (i.e., improving PFS).
- **PFS and OS:** pERC noted that venetoclax plus ibrutinib likely results in a clinically important difference in the probability of being progression free at 36 and 60 months, compared to placebo plus ibrutinib (moderate to high certainty of evidence). With regards to OS, venetoclax plus ibrutinib, compared to placebo plus ibrutinib, may result in little or no difference in the probability of being alive at 48 or 60 months (low certainty of evidence). However, the data from the interim OS analysis were immature; therefore, the effect of venetoclax plus ibrutinib on OS compared to ibrutinib alone is uncertain at this time. pERC recognized that there is a gap in the current evidence regarding OS, which may be addressed by the subsequent and final OS analyses [redacted].
- **Side effects**: pERC discussed the safety profile of venetoclax plus ibrutinib, acknowledging the patients' need for treatments that have tolerable side effects. pERC noted that venetoclax plus ibrutinib may be associated with more side effects than placebo plus ibrutinib. However, pERC agreed with the clinical experts consulted that more side effects may be expected with combination treatments and those observed with venetoclax plus ibrutinib are consistent with the known harms for the individual components of the regimen. pERC acknowledged that some patients may accept the risk of side effects given the potential for improved PFS.
- **Health-related quality of life (HRQoL)**: pERC recognized patients' need for treatments that improve quality of life. In the randomized phase of the SYMPATICO study, the Functional Assessment of

Cancer Therapy – Lymphoma (FACT-Lym) was used to measure HRQoL. pERC noted that no difference was observed between venetoclax plus ibrutinib and placebo plus ibrutinib in the FACT-Lym total score or in the score of the lymphoma-specific subscale of the FACT-Lym at 24 and 60 months. pERC noted that the certainty of evidence in HRQoL is very low and concluded that current evidence is insufficient to determine the effect of venetoclax plus ibrutinib on HRQoL relative to placebo plus ibrutinib.

- **Relevant comparators**: pERC noted that the comparative efficacy and safety evidence was available only between venetoclax plus ibrutinib and ibrutinib monotherapy. Based on clinical expert input, pERC acknowledged that ibrutinib is a standard funded second-line therapy for patients with MCL in the relapsed or refractory setting in Canada and is the main relevant comparator to venetoclax plus ibrutinib. pERC agreed with the clinical experts that the venetoclax plus ibrutinib combination therapy may change the current treatment paradigm by replacing ibrutinib monotherapy as the standard second-line treatment for most patients with MCL in the relapsed or refractory setting. Based on clinical expert input, pERC noted that some patients with relapsed or refractory MCL may receive other treatment regimens, such as bortezomib- or rituximab-based chemoimmunotherapy. However, pERC was not able to draw any conclusion on the comparative efficacy or safety, and hence the cost-effectiveness, of venetoclax plus ibrutinib versus these regimens due to lack of evidence.
- **Generalizability**: pERC noted that the randomized phase of the SYMPATICO trial required eligible patients to have at least 1 rituximab- or anti-CD20 antibody–containing regimen, while the indication approved by Health Canada does not have this requirement. pERC agreed with the clinical experts that there is no concern of generalizability to the Canadian context as all first-line therapies currently funded for patients with MCL in Canada contain an anti-CD20 antibody drug, and almost all patients would receive a rituximab- or anti-CD20 antibody–containing regimen in the first-line setting except for a small number of patients who have reasons not to (e.g., intolerance to rituximab).

## Background

MCL is a frequently aggressive subtype of B-cell NHL, accounting for approximately 5% to 7% of NHL cases. In Canada, NHL is estimated to account for 11,700 new cases in 2024, with a 5-year prevalence of 32,915 cases in 2018. MCL, although representing a small subset of NHL cases, remains a significant clinical challenge due to its aggressive nature. Nearly all patients with MCL will require systemic therapy, and the vast majority will eventually experience relapsed or refractory disease. MCL primarily affects older adults, with an average age of diagnosis between 60 and 70 years, and it occurs 4 times more frequently in men. The disease follows a progressive course, often involving the lymph nodes, bone marrow, spleen, and gastrointestinal tract. Patients typically present with symptoms such as painless lymphadenopathy, fatigue, night sweats, fever, or weight loss, which can significantly impact their HRQoL. MCL has an unfavourable prognosis, with a varying median OS of 2 to 10 years. Diagnosis of MCL requires a comprehensive clinical evaluation, including a detailed patient history, physical examination, and specialized diagnostic testing.

Diagnostic tests for MCL, including immunohistochemistry, molecular assays, and genetic testing, are widely available in Canada and are routinely used in clinical practice.

According to the clinical experts consulted by the CDA-AMC review team, MCL is not curable with most therapies, and the goal of first-line treatment is to achieve remission, delay progression, and improve survival. The choice of first-line chemoimmunotherapy is determined based on patient age, fitness, comorbidities, and institutional preferences. Younger patients (approximately up to age 65) who are medically fit and have not received prior treatment for MCL are typically treated with intensive rituximab-based chemoimmunotherapy (e.g., rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunomycin), vincristine sulfate (oncovin), and prednisone (R-CHOP) and rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP); bendamustine-rituximab and cytarabine-rituximab; bendamustine-rituximab) followed by autologous stem cell transplant and maintenance rituximab for patients with disease that responds to the treatment. Older or medically unfit patients with treatment-naive MCL are typically treated with lower-intensity chemoimmunotherapy (e.g., bendamustine-rituximab) followed by rituximab maintenance. Most patients with MCL are not cured by first-line treatments and will eventually experience disease progression and require second-line treatments. For these patients with relapsed or refractory MCL, ibrutinib, a first-generation covalent Bruton tyrosine kinase inhibitor (BTKi), is a standard second-line treatment in Canada. Zanubrutinib and acalabrutinib, second-generation BTKis, have been approved by Health Canada for relapsed or refractory MCL; however, neither of them is currently publicly funded in Canada. Most patients with MCL are also not cured by second-line treatment with ibrutinib and will be treated with third-line treatment, according to the clinical experts consulted by the CDA-AMC review team. Chimeric antigen receptor (CAR) T-cell therapy with brexucabtagene autolecleucel is a third-line standard of care treatment in Canada for selected patients with relapsed or refractory MCL who have been treated with 2 or more lines of prior systemic therapy, including a BTKi.

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of venetoclax (Venclexta), combined with ibrutinib, in the treatment of adults with MCL who have received at least 1 prior therapy.

Venetoclax is currently under review by Health Canada, in combination with ibrutinib, for the treatment of adult patients with relapsed or refractory MCL. Venetoclax is a selective and orally bioavailable small-molecule inhibitor of BCL2. It is available as 10 mg, 50 mg and 100 mg oral tablets and the dosage recommended in the product monograph for the indication is as follows: “venetoclax is taken according to a 5-week ramp-up dosing schedule in combination with ibrutinib 560 mg once daily. After completing the ramp-up phase, venetoclax is continued at a dose of 400 mg once daily in combination with ibrutinib 560 mg once daily for 23 months, followed by ibrutinib monotherapy 560 mg once daily until disease progression or unacceptable toxicity.”

## Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, double-blind RCT (the randomized phase of the SYMPATICO trial) in patients with MCL who have received at least 1, but no more than 5, prior treatment regimens for MCL, including at least 1 prior rituximab- or anti-CD20 antibody–containing regimen
- patients' perspectives gathered by 1 patient group, Lymphoma Canada
- input from the public drug plans that participate in the reimbursement review process
- 3 clinical specialists with expertise diagnosing and treating patients with MCL
- input from 2 clinician groups, the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee and the Lymphoma Canada Physician Group
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups that responded to our call for input and from the clinical experts consulted by for the purpose of this review.

### Patient Input

CDA-AMC received 1 patient group input for this review from Lymphoma Canada, which collected patient input through an online anonymous survey between January and March 2025, gathering 82 responses from patients with MCL, with 5 patients who had received venetoclax plus ibrutinib (3 from Canada). Most of all survey respondents were people from Canada (74%), aged between 65 to 74 years (36%), with diagnoses occurring 3 to 5 years ago (27%), or 9 to 10 years ago or more (24%).

The survey respondents reported that MCL had significant impacts on their quality of life, with 28% reporting fatigue and 15% experiencing neutropenia. Patients also reported psychological challenges (with 72% experiencing stress, 70% anxiety, and 64% fear of progression) as well as mental health challenges (with 74% reporting fear of relapse and 38% having difficulty sleeping). Daily life was impacted by factors such as the ability to travel (38%), work (28%), and engage in social activities (20%), with many patients highlighting the challenges of managing a compromised immune system, isolation, and physical limitations due to treatment side effects.

Regarding current treatments for MCL, most respondents (56%) received 1 line of treatment. In the second line or beyond, 29% of the respondents received stem cell transplants and 15% received BTKis. While 78% were satisfied with front-line treatments, satisfaction dropped for second-line (27%) and third-line (13%) options, indicating a need for more alternatives. Side effects such as fatigue, nausea, and joint pain were common and severely impacted patients' quality of life. Patients expressed their desire to have more treatment options, especially for second- and third-line therapies.

Patients with MCL surveyed by Lymphoma Canada highlighted key outcomes of new treatments, including longer disease remission, survival, quality of life, and symptom control. A majority (91%) were willing to tolerate mild, short-term side effects for better options, and 76% valued having treatment choices based on side effects and outcomes.

Five patients in the survey received combination of venetoclax plus ibrutinib in the second-line setting, with 1 in new remission, 3 in remission for 1 to 2 years, and 1 relapsing after treatment. Reported side effects included diarrhea (3 patients), neutropenia (2 patients), fatigue (2 patients), joint pain (1 patient), and constipation (1 patient). Psychological impacts included anxiety (3 patients) and fear of progression (2 patients).

## Clinician Input

### Input From Clinical Experts Consulted for This Review

The clinical experts consulted by the CDA-AMC review team noted that the goal of first-line treatment for MCL is to achieve remission, delay progression, and improve survival. Treatments for patients with relapsed or refractory MCL are usually not curative, and most patients will eventually experience disease progression. The clinical experts noted that ibrutinib was a standard second-line treatment for patients with MCL who have relapsed or are refractory to first-line treatments, but most patients who have disease that responds to ibrutinib would progress eventually. Therefore, there is an unmet need for treatments with long-lasting benefits that are well-tolerated for patients with relapsed or refractory MCL in the second-line treatment setting.

All of the clinical experts agreed that venetoclax plus ibrutinib should become a standard second-line treatment for patients with relapsed or refractory MCL and also noted that ibrutinib plus venetoclax may change the current treatment paradigm by replacing ibrutinib monotherapy as the standard second-line treatment for most patients with relapsed or refractory MCL. The clinical experts consulted by the CDA-AMC review team noted that ibrutinib monotherapy could remain as an alternative treatment option in the second-line treatment setting for some patients.

The clinical experts noted that patients who are best suited for venetoclax plus ibrutinib are those who have relapsed or refractory MCL and have received at least 1 prior line of therapy. The clinical experts indicated that patients whose disease is refractory to BTK or BCL2 inhibitors may not be suitable for venetoclax plus ibrutinib, nor would patients who are unable or unwilling to perform bloodwork for tumour lysis monitoring; patients with serious active infections, severe liver dysfunction, or inability to swallow or absorb oral medications; patients who require ongoing treatment with moderate or strong CYP3A inhibitors or inducers; or those with relative contraindications to ibrutinib (e.g., uncontrolled cardiovascular disease).

Assessing response to venetoclax plus ibrutinib, which may vary between physicians and institutions, generally includes a radiographic assessment after 2 to 3 months of treatment. Patients with circulating lymphoma cells and/or bone marrow involvement may have a complete blood count with or without bone marrow sampling done as part of response assessment, and for patients whose disease demonstrates a response to venetoclax plus ibrutinib, treatment is continued for up to 2 years with venetoclax plus ibrutinib

followed by ibrutinib monotherapy until disease progression or unacceptable intolerance. Subsequent imaging would depend on the depth of initial response and the discretion of the treating physician.

According to the clinical experts, venetoclax should be given for a fixed duration course of up to 2 years, while ibrutinib should be continued indefinitely. Either drug may be discontinued earlier for patients who experience disease progression or develop refractory disease while on treatment, or for those who experience unacceptable toxicities. The clinical experts noted that in the real-world setting where discontinuation occurs due to disease progression, treatment may be continued while planning for next line of therapy to prevent disease progression. The clinical experts noted that when 1 drug is discontinued due to intolerance, it does not necessarily mean the other drug should also be discontinued at the same time, as ibrutinib and venetoclax have different side effect profiles, and the decision to discontinue either or both drugs should be made by the treating physician.

According to the clinical experts consulted by the CDA-AMC review team, venetoclax plus ibrutinib should be prescribed by a hematologist or oncologist who is familiar with the management of MCL and has knowledge regarding the safety, efficacy, and monitoring requirements of each drug, particularly regarding the risk of tumour lysis syndrome with venetoclax and the cardiovascular toxicities of ibrutinib. Treatment with venetoclax plus ibrutinib (including the ramp-up phase of venetoclax) can be administered in the outpatient setting at both tertiary care and community hospitals in both urban and rural locations.

### Clinician Group Input

CDA-AMC received input from 2 clinician groups, the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee and the Lymphoma Canada Physician Group. The Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee provided input via teleconference with 7 clinicians. The Lymphoma Canada Physician Group reviewed clinical trials, provincial guidelines, and shared a review on relapsed or refractory MCL with 5 experts.

According to the clinician groups, the goal of therapy for patients with MCL is long-term PFS and OS, resolution of lymphoma-related symptoms, and improvement in quality of life. The clinician groups noted that treatment for patients with relapsed or refractory MCL includes BTKis (i.e., ibrutinib, acalabrutinib, zanubrutinib, and pirtobrutinib), chemoimmunotherapy, and bortezomib-based options. The groups highlighted that while BTKis are standard second-line therapy, their effectiveness declines, and relapse after a BTKi remains a major unmet need. Both clinician groups highlighted significant treatment gaps for relapsed or refractory MCL as no curative therapies exist. Current treatments offer limited survival benefits, with poor outcomes after BTKi failure; for example, average survival is under 6 months. The Lymphoma Canada Physician Group noted that while CAR T-cell therapy (brexucabtagene autolecleucel) is now funded in Canada, access remains restricted to specialized centres and select patients. Most patients with MCL who experience relapse do not qualify, leaving palliative options as the only alternative. There is a critical need for novel, well-tolerated treatment combinations to improve survival, delay disease progression, and enhance quality of life for the majority of patients.

The clinician groups noted that venetoclax plus ibrutinib is suitable as a second-line treatment option for relapsed or refractory MCL. According to the clinician groups, suitable candidates include patients eligible for

BTKi treatment, particularly those who are not BTKi refractory. They further noted that as a fully oral therapy, the combination of venetoclax and ibrutinib is suited for outpatient care and accessible in both community and academic settings and should be prescribed by a hematologist managing MCL.

## Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

### Table 2: Responses to Questions From the Drug Programs

| Implementation questions | Response |
|---|---|
| **Relevant comparators** | |
| For patients with relapsed or refractory MCL, treatment with a BTKi is 1 current standard of therapy in Canada.<br>Ibrutinib is the only BTKi publicly reimbursed in Canada for patients with MCL who have received at least 1 prior therapy. Although acalabrutinib and zanubrutinib are both approved by Health Canada for relapsed or refractory MCL, acalabrutinib has not been reviewed by CDA-AMC and zanubrutinib received a negative recommendation due to the uncertainty associated with the 2 phase II single-arm trials assessed. Public reimbursement of ibrutinib for relapsed or refractory MCL was supported by the results of the phase III randomized controlled trial MCL-3001.<br>The SYMPATICO trial compared venetoclax-ibrutinib against ibrutinib in patients with MCL after 1 to 5 prior lines of therapy, including 1 prior rituximab- or anti-CD20 antibody–containing regimen.<br>Rituximab-bendamustine in relapsed or refractory MCL is also a funded option in some jurisdictions. | This is a comment from the drug plans to inform pERC deliberations. |
| **Considerations for prescribing of therapy** | |
| Venetoclax included a 5-week ramp-up beginning on day 1, at a dosage of 20 mg, 50 mg, 100 mg, 200 mg, and 400 mg once daily for weeks 1 to 5, respectively. After completing the ramp-up, venetoclax 400 mg once daily was continued until disease progression or unacceptable toxicity for a total treatment duration of 24 months. Ibrutinib 560 mg once daily was taken in combination with venetoclax for a 24-month period, with single-drug ibrutinib 560 mg once daily continued beyond 24 months until disease progression or unacceptable toxicity. | This is a comment from the drug plans to inform pERC deliberations. |
| In-patient administration may be required during the first few ramp-up doses for patients at high risk for tumour lysis syndrome. | This is a comment from the drug plans to inform pERC deliberations. |
| In the SYMPATICO trial, if 1 study drug had to be discontinued, the participant was allowed to continue in the trial and receive the other study drug.<br>**Question**: If a patient experiences intolerance to ibrutinib, can treatment with venetoclax monotherapy be continued? | pERC agreed with the clinical experts that, when 1 drug is discontinued due to intolerance, it does not necessarily mean the other drug should also be discontinued at the same time, as ibrutinib and venetoclax have different toxicity profiles. The clinical experts noted that the decision to discontinue either or both drugs should be made at the clinician's discretion. |

| Implementation questions | Response |
|---|---|
| **Generalizability** | |
| Patients with an ECOG PS of 0 to 2 were included in the SYMPATICO trial.<br>**Question**: Can patients with an ECOG PS of 3 be considered eligible? | Two of the clinical experts consulted noted that selected patients with an ECOG PS of 3 can be considered eligible for venetoclax plus ibrutinib, while the third clinical expert indicated that individuals with an ECOG PS of 3 may benefit more from therapies with a palliative intent rather than venetoclax plus ibrutinib, given the added toxicity of the combination.<br>The 2 clinical experts who supported the use of venetoclax plus ibrutinib in selected patients with an ECOG PS of 3 noted that a patient with worse performance status does not necessarily mean the patient is not eligible for venetoclax plus ibrutinib, and the decision on eligibility should be made on a case-by-case basis. For example, some patients have poor a ECOG PS due to disease-related symptoms, which may improve with treatment.<br>pERC agreed that venetoclax plus ibrutinib can be used in patients with an ECOG PS of 3 at the clinician's discretion. |
| **Question**: On a time-limited basis, should patients currently receiving ibrutinib or other alternative treatments be eligible to switch to venetoclax plus ibrutinib? | pERC agreed with the clinical experts who indicated that if a patient is currently stable and their disease is responding well to a treatment (e.g., ibrutinib or other alternative treatments), in most cases they would not switch them to venetoclax plus ibrutinib. However, pERC agreed with the clinical experts that switching patients to ibrutinib plus venetoclax or adding venetoclax (for those receiving ibrutinib monotherapy), if are early in their treatment course (i.e., started treatment recently, within the preceding 6 months) and show no evidence of disease progression, can be considered.<br>pERC agreed with the clinical experts who indicated that if a patient has disease progression while on treatment with ibrutinib, there are no data to support adding venetoclax to ibrutinib, or to any other covalent BTKi-containing regimen in the next line of therapy. |
| **Funding algorithm** | |
| There are upcoming reviews for MCL, so an algorithm will be helpful; these include:<br>• acalabrutinib, rituximab, and bendamustine for first-line transplant-ineligible MCL<br>• ibrutinib, rituximab, and chemotherapy for first-line transplant-eligible MCL. | This is a comment from the drug plans to inform pERC deliberations. |
| **Care provision issues** | |
| Venetoclax is available as 10 mg, 50 mg, and 100 mg tablets. The product monograph indicates it can be stored between 2°C and 30°C. | This is a comment from the drug plans to inform pERC deliberations. |
| Venetoclax has the potential for drug-drug, drug-food, and drug-herb interactions. | This is a comment from the drug plans to inform pERC deliberations. |

| Implementation questions | Response |
|---|---|
| **System and economic issues** | |
| The budget impact is uncertain given the upcoming reviews for BTKi-based regimens in the front-line space, which may lessen the uptake for venetoclax plus ibrutinib. However, this may be offset by the combination use of venetoclax plus ibrutinib (up to 2 years) followed by the use of single-drug ibrutinib until disease progression or unacceptable toxicity. | This is a comment from the drug plans to inform pERC deliberations. |

BTKi = Bruton tyrosine kinase inhibitor; CDA-AMC = Canada's Drug Agency; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MCL = mantle cell lymphoma; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

# Clinical Evidence

## Systematic Review

### Description of Studies

One study (SYMPATICO) was identified from the sponsor-submitted systematic literature review. The SYMPATICO trial consisted of an open-label safety run-in phase, a double-blind randomized phase, and an open-label treatment-naive cohort. The primary focus for this review is the randomized phase of SYMPATICO, which was a phase III, multicentre, double-blind RCT, investigating the efficacy and safety of venetoclax plus ibrutinib in patients with MCL who had received at least 1, but no more than 5, prior treatment regimens for MCL, including at least 1 prior rituximab- or anti-CD20 antibody–containing regimen. A total of 267 patients (including [redacted] patients in Canada) were randomized to the venetoclax plus ibrutinib group (n = 134) and the placebo plus ibrutinib group (n = 133). The primary objective of the randomized phase of the SYMPATICO trial was to assess the efficacy of venetoclax plus ibrutinib relative to placebo plus ibrutinib as measured by PFS per investigator assessment. Secondary end points included OS and harms. HRQoL outcomes, such as FACT-Lym total score and lymphoma-specific subscale of the FACT-Lym score, were also reported.

Patients in the intention-to-treat (ITT) population of the randomized phase of the SYMPATICO trial had a median age of 68 years (range, 42 to 88). There were more male patients than female patients (79.0% versus 21.0%). Most patients were white (86.5%), followed by Asian (1.9%) and Black or African American (0.7%). Approximately 59.6%, 23.6%, and 16.9% of the ITT population had received 1, 2, or 3 or more lines of therapies before receiving venetoclax plus ibrutinib, respectively.

### Efficacy Results

The data cut-off date was May 22, 2023 (database lock date: July 5, 2023). The median time on study was [redacted] (range, [redacted] to [redacted]) for the venetoclax plus ibrutinib group and [redacted] months (range, [redacted] to [redacted]) for the placebo plus ibrutinib group.

### *Overall Survival*

In the interim analysis of OS, the proportion of the ITT population who had OS events was 51.5% in the venetoclax plus ibrutinib group versus 56.4% in the placebo plus ibrutinib group. The median OS was 44.9 months (95% CI, 31.9 to not estimable) in the venetoclax plus ibrutinib group versus 38.6 months (95% CI, 25.2 to 53.4) in the placebo plus ibrutinib group. The HR for death was 0.854 (95% CI, 0.615 to 1.186). At 12 months, the probability of being alive was [redacted] (95% CI, [redacted] to [redacted]) for the venetoclax plus ibrutinib group and [redacted] (95% CI, [redacted] to [redacted]) for the placebo plus ibrutinib group (between-group difference = [redacted]; 95% CI, [redacted] to [redacted]). At 24 months, the probability of being alive was 65.9% (95% CI, 57.2 to 73.3) for the venetoclax plus ibrutinib group and 61.4% (95% CI, 52.5 to 69.1) for the placebo plus ibrutinib group (between-group difference = 4.5%; 95% CI, −7.0 to 16.2). At 36 months, the probability of being alive was [redacted] (95% CI, [redacted] to [redacted]) for the venetoclax plus ibrutinib group and [redacted] (95% CI, [redacted] to [redacted]) for the placebo plus ibrutinib group (between-group difference = [redacted]; 95% CI, [redacted] to [redacted]). At 48 months, the probability of being alive was [redacted] (95% CI, [redacted] to [redacted]) for the venetoclax plus ibrutinib group and [redacted] (95% CI, [redacted] to [redacted]) for the placebo plus ibrutinib group (between-group difference = [redacted]; 95% CI, [redacted] to [redacted]). At 60 months, the probability of being alive was [redacted] (95% CI, [redacted] to [redacted]) for the venetoclax plus ibrutinib group and [redacted] (95% CI, [redacted] to [redacted]) for the placebo plus ibrutinib group (between-group difference = [redacted]; 95% CI, [redacted] to [redacted]).

### *PFS Per Investigator Assessment*

The proportion of the ITT population who had PFS events was 54.5% in the venetoclax plus ibrutinib group and 70.7% in the placebo plus ibrutinib group. The median PFS per investigator assessment was 31.9 months (95% CI, 22.8 to 47.0) in the venetoclax plus ibrutinib group versus 22.1 months (95% CI, 16.5 to 29.5) in the placebo plus ibrutinib group. The HR for PFS per investigator assessment was 0.645 (95% CI, 0.474 to 0.878). At 12 months, the probability of being progression free was [redacted] (95% CI, [redacted] to [redacted]) for the venetoclax plus ibrutinib group and [redacted] (95% CI, [redacted] to [redacted]) for the placebo plus ibrutinib group (between-group difference = [redacted] 95% CI, [redacted] to [redacted]). At 24 months, the probability of being progression free was 56.8% (95% CI, 47.7 to 64.9) for the venetoclax plus ibrutinib group and 45.4% (95% CI, 36.5 to 53.8) for the placebo plus ibrutinib group (between-group difference = 11.4%; 95% CI, −0.8 to 23.7). At 36 months, the probability of being progression free was [redacted] (95% CI, [redacted] to [redacted]) for the venetoclax plus ibrutinib group and [redacted] (95% CI, [redacted] to [redacted]) for the placebo plus ibrutinib group (between-group difference = [redacted]; 95% CI, [redacted] to [redacted]). At 48 months, the probability of being progression free was [redacted] (95% CI, [redacted] to [redacted]) for the venetoclax plus ibrutinib group and [redacted] (95% CI, [redacted] to [redacted]) for the placebo plus ibrutinib group (between-group difference = [redacted]; 95% CI, [redacted] to [redacted]). At 60 months, the probability of being progression free was [redacted] (95% CI, [redacted] to [redacted]) for the venetoclax plus ibrutinib group and [redacted] (95% CI, [redacted] to [redacted]) for the placebo plus ibrutinib group (between-group difference = [redacted]; 95% CI, [redacted] to [redacted]).

The overall concordance for PFS events was [redacted] for the venetoclax plus ibrutinib group and [redacted] for the placebo plus ibrutinib group.

### *FACT-Lym Total Score*

The FACT-Lym total score ranges between 0 and 168, with a higher score indicating a better HRQoL.

The difference in change from baseline FACT-Lym total score between the venetoclax plus ibrutinib group and the placebo plus ibrutinib group was [redacted] (95% CI, [redacted] to [redacted]) at [redacted] and [redacted] (95% CI, [redacted] to [redacted]) at [redacted].

### *Lymphoma-Specific Subscale of the FACT-Lym Score*

The lymphoma-specific subscale of the FACT-Lym score ranges between 0 and 60, with a higher score indicating a better HRQoL.

The difference in change from baseline score in the lymphoma-specific subscale of the FACT-Lym between the venetoclax plus ibrutinib group and the placebo plus ibrutinib group was [redacted] (95% CI, [redacted] to [redacted]) at 24 months and [redacted] (95% CI, [redacted] to [redacted]) at 60 months.

## Harms Results

The proportion of patients who had a grade 3 or higher treatment-emergent adverse event (TEAE) was 83.6% in the venetoclax plus ibrutinib group versus 75.8% in the placebo plus ibrutinib group. The most common grade 3 or higher TEAEs included neutropenia (31.3% in the venetoclax plus ibrutinib group versus 10.6% in the placebo plus ibrutinib group), pneumonia (12.7% in the venetoclax plus ibrutinib group versus 10.6% in the placebo plus ibrutinib group), thrombocytopenia (12.7% in the venetoclax plus ibrutinib group versus 7.6% in the placebo plus ibrutinib group), and worsening of MCL (6.7% in the venetoclax plus ibrutinib group versus 12.1% in the placebo plus ibrutinib group).

The proportion of patients who had a treatment-emergent serious adverse event (TESAE) was 60.4% in the venetoclax plus ibrutinib group versus 59.8% in the placebo plus ibrutinib group. The most common TESAE was pneumonia (12.7% in the venetoclax plus ibrutinib group versus 10.6% in the placebo plus ibrutinib group), followed by worsening of MCL (6.7% in the venetoclax plus ibrutinib group versus 12.9% in the placebo plus ibrutinib group).

Discontinuation of venetoclax or placebo due to a TEAE occurred in 22.4% of the patients in the venetoclax plus ibrutinib group versus 28.8% in the placebo plus ibrutinib group. Discontinuation of ibrutinib due to a TEAE occurred in 29.1% of the patients in the venetoclax plus ibrutinib group versus 31.1% in the placebo plus ibrutinib group. The proportion of patients with any adverse event (AE) with the outcome of death was 16.4% in the venetoclax plus ibrutinib group versus 13.6% in the placebo plus ibrutinib group. The most common reason was worsening of MCL (3.0% in the venetoclax plus ibrutinib group versus 7.6% in the placebo plus ibrutinib group).

Treatment-emergent major hemorrhage, which included serious or grade 3 or higher hemorrhage and central nervous system hemorrhage of any grade among bleeding event, occurred in [redacted] of the patients in the venetoclax plus ibrutinib group versus [redacted] in the placebo plus ibrutinib group. Atrial fibrillation of any grade occurred in 10.4% of the patients in the venetoclax plus ibrutinib group versus 10.6% in the placebo plus ibrutinib group. The percentage of patients who had cardiac arrhythmias (excluding atrial fibrillation) of

any grade was [redacted] in the venetoclax plus ibrutinib group versus [redacted] in the placebo plus ibrutinib group. The percentage of patients who had tumour lysis syndrome of any grade was 5.2% in the venetoclax plus ibrutinib group versus 2.3% in the placebo plus ibrutinib group. In total, there were 3 deaths potentially due to cardiac-related causes in the venetoclax plus ibrutinib group and 1 death in the placebo plus ibrutinib group.

## Critical Appraisal

### *Internal Validity*

In the randomized phase of the SYMPATICO trial, only results from the interim OS analysis were available for this review, which was considered immature as the upper bound of the 95% CI of the median OS in the venetoclax plus ibrutinib group was not estimable. As a result, uncertainty remains in the interim OS evidence, which may be addressed by the final OS analysis. [redacted]. Two sets of censoring rules were used to estimate PFS, the global censoring rules for the primary analysis and the FDA censoring rules for 1 of the sensitivity analyses. In the global censoring rules, patients without progression or death were censored, while in the FDA censoring rules, 2 additional censoring scenarios were added on top of the global censoring rules (i.e., patients without progressive disease or death, those with subsequent anticancer therapy, or those with 2 or more missed visits before the PFS event were censored). There was a large difference in median PFS in the venetoclax plus ibrutinib group (approximately a 10-month increase) but not in the placebo plus ibrutinib group (no change) between the primary PFS analysis (i.e., per the global censoring rules) and the PFS sensitivity analysis (i.e., per the FDA censoring rules), as noted by the review team and other researchers. This indicated that the patients in the venetoclax plus ibrutinib group who were censored by the additional 2 scenarios of the FDA rules were not equally likely to experience disease progression when compared to those who were not censored. Specifically, the additionally censored patients in the venetoclax plus ibrutinib group were at a higher risk, which would have violated the noninformative censoring assumption of the Kaplan-Meier method, skewed the Kaplan-Meier curve, and resulted in an overestimation of median PFS in the analysis with the FDA censoring rules. Moreover, as Lesan et al. (2024) pointed out, the possibility of overestimation in the PFS primary analysis using the global censoring rules could also not be ruled out because, for example, in the primary PFS analysis, patients who missed visits were not censored. Given that these patients were potentially at a higher risk of developing disease progression (as suggested by the sensitivity analysis using the FDA censoring rules), not counting these patients as having a PFS event may have overestimated the median PFS. There was a potential risk of unblinding in patients or investigators due to a higher occurrence of digestive AEs in the venetoclax plus ibrutinib group compared to in the placebo plus ibrutinib group and the fact that a higher percentage of patients in the venetoclax plus ibrutinib group were treated for these digestive AEs. If patients became unblinded, there was a risk of bias in the assessment of HRQoL outcomes. There was also a risk of missing outcomes data for HRQoL outcomes. For instance, around half of the ITT population was missing when assessing the FACT-Lym total score and the lymphoma-specific subscale of the FACT-Lym score at 24 months. There was no description of how the

missing data were handled for the HRQoL outcomes; therefore, it is uncertain how the missing HRQoL data impacted the observed results.

### *External Validity*

The eligibility criteria of the randomized phase of the SYMPATICO trial were generally aligned with the selection criteria in the Canadian setting when identifying eligible patients with MCL in the relapsed and refractory setting, according to the clinical experts consulted by the review team. However, the clinical experts noted that some patients who might benefit from venetoclax plus ibrutinib were not included in the randomized phase of the SYMPATICO trial, including selected patients with an Eastern Cooperative Oncology Group Performance Status greater than 2; patients who have previously been exposed to, but did not have disease that was refractory, to venetoclax or ibrutinib; patients without at least 1 site of 2.0 cm disease (e.g., leukemic MCL), and patients with rare central nervous system involvement by MCL. Nonetheless, the results from the randomized phase of the SYMPATICO trial were still likely to be generalizable to the previously mentioned patients. According to the inclusion criteria of the randomized phase of the SYMPATICO trial, eligible patients were required to have received at least 1, but no more than 5, prior treatment regimens for MCL. Of the 267 patients randomized, all had received at least 1 line of anticancer therapy before receiving venetoclax plus ibrutinib. The population indicated in the proposed Health Canada indication and the reimbursement request proposed by the sponsor refers to patients with relapsed or refractory MCL, which is broader than either the intended study population of the randomized phase of the SYMPATICO trial (i.e., who received at least 1, but no more than 5, prior treatment regimens for MCL) or the patients actually included in the randomized phase of the SYMPATICO trial (i.e., who had received at least 1 prior line of anticancer therapy). In the correspondence received by CDA-AMC on April 16, 2025, the sponsor confirmed that the reimbursement request focuses on patients with MCL who have received at least 1 prior line of therapy. Similar to the sponsor's interpretation, the clinical experts consulted by the review team noted that venetoclax plus ibrutinib should be placed as the second-line standard of care treatment in the relapsed or refractory setting for patients with MCL, which will also be the most common scenario in Canada, although some patients may instead receive it in a later line of therapy at the discretion of the treating physician.

## GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based

on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for OS and PFS per investigator assessment were set according to the presence of an important effect based on thresholds agreed upon by the clinical experts consulted for this review. The reference points for the certainty of evidence assessment for the FACT-Lym total score, the lymphoma-specific subscale of the FACT-Lym score, and harms events were set according to the presence of any non-null effect.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with the expert committee members:

- survival outcomes (OS, PFS per investigator assessment)
- HRQoL outcomes (FACT-Lym total score, lymphoma-specific subscale of the FACT-Lym score)
- harms (TESAEs).

### Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for venetoclax plus ibrutinib versus placebo plus ibrutinib for patients with MCL who have received at least 1, but no more than 5, prior treatment regimens.

## Table 3: Summary of Findings for Venetoclax Plus Ibrutinib vs. Placebo Plus Ibrutinib for Patients With MCL Who Have Received At Least 1, But No More Than 5, Prior Treatment Regimens

| Outcome and follow-up | Patients (studies), N | Relative effect (95% CI) | Absolute effect (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Placebo plus Ibrutinib | Venetoclax plus Ibrutinib | Difference | | |
| **OS (interim analysis, data cut-off date: May 22, 2023)** | | | | | | | |
| **Probability of being alive at 48 months**<br>Median follow-up duration ([redacted]):<br>• [redacted] (range, [redacted] to [redacted]) for the venetoclax plus ibrutinib group<br>• [redacted] (range, [redacted] to [redacted]) for the placebo plus ibrutinib group | 267<br>(1 RCT) | [redacted] | [redacted] per 1,000 | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | Low[a] | Venetoclax plus ibrutinib may result in little or no difference in the probability of being alive at 48 months, compared to placebo plus ibrutinib. |
| **Probability of being alive at 60 months**<br>Median follow-up duration ([redacted]):<br>• [redacted] (range, [redacted] to [redacted]) for the venetoclax plus ibrutinib group<br>• [redacted] (range, [redacted] to [redacted]) for the placebo plus ibrutinib group | 267<br>(1 RCT) | [redacted] | [redacted] per 1,000 | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | Low[a] | Venetoclax plus ibrutinib may result in little or no difference in the probability of being alive at 60 months, compared to placebo plus ibrutinib. |

| Outcome and follow-up | Patients (studies), N | Relative effect (95% CI) | Absolute effect (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Placebo plus Ibrutinib | Venetoclax plus Ibrutinib | Difference | | |
| **PFS per investigator assessment (data cut-off date: May 22, 2023)** | | | | | | | |
| **Probability of being progression free at 36 months**<br>Median follow-up duration (months):<br>• [redacted] (range, [redacted] to [redacted]) for the venetoclax plus ibrutinib group<br>• [redacted] (range, [redacted] to [redacted]) for the placebo plus ibrutinib group | 267<br>(1 RCT) | [redacted] | [redacted] per 1,000 | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | Moderate[b] | Venetoclax plus ibrutinib likely results in a clinically important difference in the probability of being progression free at 36 months, compared to placebo plus ibrutinib. |
| **Probability of being progression free at 60 months**<br>Median follow-up duration (months):<br>• [redacted] (range, [redacted] to [redacted]) for the venetoclax plus ibrutinib group<br>• [redacted] (range, [redacted] to [redacted]) for the placebo plus ibrutinib group | 267<br>(1 RCT) | [redacted] | [redacted] per 1,000 | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | High[c] | Venetoclax plus ibrutinib results in a clinically important difference in the probability of being progression free at 60 months, compared to placebo plus ibrutinib. |
| **FACT-Lym total score (data cut-off date: May 22, 2023)** | | | | | | | |
| **Mean change from baseline in the FACT-Lym total score** | [redacted]<br>([redacted] RCT) | [redacted] | [redacted] (SD = [redacted]) | [redacted] (SD = [redacted]) | [redacted] ([redacted] to [redacted]) | Very low[d] | The evidence is uncertain about the effect of venetoclax plus ibrutinib on |

| Outcome and follow-up | Patients (studies), N | Relative effect (95% CI) | Absolute effect (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Placebo plus Ibrutinib | Venetoclax plus Ibrutinib | Difference | | |
| (0 [worst] to 168 [best])<br>Follow-up: 24 months | | | | | | | the FACT-Lym total score at 24 months, compared to placebo plus ibrutinib. |
| **Mean change from baseline in the FACT-Lym total score**<br>(0 [worst] to 168 [best])<br>Follow-up: 60 months | [redacted] ([redacted] RCT) | [redacted] | [redacted] (SD = [redacted]) | [redacted] (SD = [redacted]) | [redacted] ([redacted] to [redacted]) | Very low[d] | The evidence is uncertain about the effect of venetoclax plus ibrutinib on the FACT-Lym total score at 60 months, compared to placebo plus ibrutinib. |
| **Lymphoma-specific subscale of the FACT-Lym score (data cut-off date: May 22, 2023)** | | | | | | | |
| **Mean change from baseline in the lymphoma-specific subscale of the FACT-Lym score**<br>(0 [worst] to 60 [best])<br>Follow-up: 24 months | [redacted] ([redacted] RCT) | [redacted] | [redacted] (SD = [redacted]) | [redacted] (SD = [redacted]) | [redacted] ([redacted] to [redacted]) | Very low[d] | The evidence is uncertain about the effect of venetoclax plus ibrutinib on the lymphoma-specific subscale of the FACT-Lym score at 24 months, compared to placebo plus ibrutinib. |
| **Mean change from baseline in the lymphoma-specific subscale of the FACT-Lym score**<br>(0 [worst] to 60 [best])<br>Follow-up: 60 months | [redacted] ([redacted] RCT) | [redacted] | [redacted] (SD = [redacted]) | [redacted] (SD = [redacted]) | [redacted] ([redacted] to [redacted]) | Very low[d] | The evidence is uncertain about the effect of venetoclax plus ibrutinib on the lymphoma-specific subscale of the FACT-Lym score at 60 months, compared to placebo plus ibrutinib. |

| Outcome and follow-up | Patients (studies), N | Relative effect (95% CI) | Absolute effect (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Placebo plus Ibrutinib | Venetoclax plus Ibrutinib | Difference | | |
| **Harms (data cut-off date: May 22, 2023)** | | | | | | | |
| **TESAEs**<br>Follow-up: 60 months | [redacted] ([redacted] RCT) | [redacted] | [redacted] per 1,000 | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | [redacted] per 1,000 ([redacted] to [redacted] per 1,000) | Low[e] | Venetoclax plus ibrutinib may result in little or no difference in TESAEs, compared to placebo plus ibrutinib. |

CDA-AMC = Canada's Drug Agency; CI = confidence interval; FACT-Lym = Functional Assessment of Cancer Therapy – Lymphoma; MCL = mantle cell lymphoma; MID = minimal important difference; NR = not reported; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; SD = standard deviation; TESAE = treatment-emergent serious adverse event; vs. = versus.

Notes: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the following footnotes.

[a]Rated down 2 levels for very serious imprecision. According to the clinical experts consulted by the CDA-AMC review team, a 5% difference (50 per 1,000) between the venetoclax plus ibrutinib group and the placebo plus ibrutinib group in the probability of being alive could be considered clinically important (i.e., MID). The point estimate suggested little to no difference while the upper and lower bounds of the 95% CI crossed the MID and the null (i.e., 0), respectively.

[b]Rated down 1 level for serious imprecision. According to the clinical experts consulted by the CDA-AMC review team, a 7% (70 per 1,000) difference between the venetoclax plus ibrutinib group and the placebo plus ibrutinib group in the probability of being progression free could be considered clinically important (i.e., MID). The point estimate suggested benefits while the upper bound of the 95% CI crossed the MID.

[c]Certainty of evidence was not rated down as there were no serious concerns in risk of bias, indirectness, inconsistency, or imprecision.

[d]Rated down 2 levels for serious risk of bias. Although the randomized phase of the SYMPATICO trial adopted a double-blind study design, there was a risk of unblinding due to the high between-group imbalance in the occurrence of some adverse events, such as diarrhea (64.9% vs. 34.1%) and nausea (31.3% vs. 16.7%). Moreover, there was a risk of bias due to missing data from a high percentage of patients. Rated down 2 levels for very serious imprecision as the 95% CIs of the mean difference crossed the null threshold of 0.

[e]Rated down 2 levels for imprecision. The 95% CI crossed the null, suggesting both benefit and harm.

Sources: SYMPATICO Clinical Study Report,[28] sponsor response to CDA-AMC request for additional information.

### Long-Term Extension Studies
No long-term extension studies were identified for this review.

### Indirect Comparisons
No indirect evidence was identified for this review.

### Studies Addressing Gaps in the Evidence From the Systematic Review
No studies addressing gaps in the pivotal and RCT evidence were identified for this review.

## Economic Evidence

### Cost and Cost-Effectiveness
- Venetoclax is supplied as 10 mg, 50 mg, and 100 mg tablets. At the submitted unit price, the cost of venetoclax is $1,834 per patient in the first 28-day cycle (subsequent cycles = $7,930), based on the Health Canada–recommended dosage. When used in combination with ibrutinib, the total cost is $13,016 per patient in the first 28-day cycle and $19,111 in subsequent cycles. The total recommended duration of venetoclax treatment is 24 months.
- The clinical efficacy data used in the economic analysis were derived from the randomized phase of the SYMPATICO trial, which compared venetoclax plus ibrutinib to placebo plus ibrutinib. Evidence from the SYMPATICO trial suggests that venetoclax plus ibrutinib likely results in a clinically meaningful improvement in the probability of being progression free at 60 months compared to ibrutinib alone, with little to no difference in survival at 60 months.
- The results of the CDA-AMC base case suggest:
  - Venetoclax plus ibrutinib is predicted to be associated with higher costs to the health care system than ibrutinib alone (incremental costs = $172,576), primarily driven by the increased acquisition costs associated with venetoclax.
  - Venetoclax plus ibrutinib is predicted to be associated with an incremental gain of 0.51 life-years compared to ibrutinib alone and may result in a gain of 0.48 QALYs compared to ibrutinib alone.
  - The ICER for venetoclax plus ibrutinib versus ibrutinib alone was $360,148 per QALY gained in the CDA-AMC base case. The estimated ICER was highly sensitive to the predicted OS benefit, and more than 85% of the incremental benefit was gained in the extrapolated period (i.e., after 60 months). In the absence of long-term data, these projected benefits are highly uncertain and may be overestimated. Additional price reductions may therefore be required.
- CDA-AMC estimates that the budget impact of reimbursing venetoclax for use in combination with ibrutinib for relapsed or refractory MCL will be approximately $43 million over the first 3 years of reimbursement compared to the amount currently spent on ibrutinib alone. The expenditure on venetoclax over this period is predicted to be approximately $40 million. The actual budget impact of

reimbursing venetoclax will depend on the number of eligible patients, market uptake, and the use of other treatments.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

# pERC Information

## Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan, 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. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

**Meeting date**: July 9, 2025

**Regrets**: Three 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.