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Reimbursement Recommendation

Ibrutinib

Reimbursement request: In combination with immunochemotherapy with or without autologous stem cell transplant for previously untreated transplant-eligible patients with mantle cell lymphoma

Requester: Public drug programs

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Ibrutinib?

The Formulary Management Expert Committee (FMEC) recommends that ibrutinib in combination with immunochemotherapy with or without autologous stem cell transplant (ASCT) be reimbursed for previously untreated, transplant-eligible patients with mantle cell lymphoma (MCL), provided certain conditions are met.

What Are the Conditions for Reimbursement?

Ibrutinib in combination with immunotherapy with or without ASCT may be initiated in adults for the treatment of MCL if they meet the following conditions: they are an adult patient with untreated MCL, they are deemed transplant-eligible, and they have good performance status. A price reduction may be required.

Why Did Canada's Drug Agency Make This Recommendation?

FMEC reviewed the Canada's Drug Agency (CDA-AMC) report, which included a review of the clinical evidence, specifically the TRIANGLE trial and a cost comparison of ibrutinib versus other treatments used in Canada. The TRIANGLE trial was a randomized, controlled, phase III, 3-arm, open-label trial comparing ibrutinib plus rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP) and rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) or ASCT (group A + I) to alternating R-CHOP and R-DHAP with ASCT (group A) and to ibrutinib plus alternating R-CHOP and R-DHAP without ASCT (group I) for patients with untreated MCL who were transplant-eligible. Based on the comparison of group A + I to group A, ibrutinib combined with alternating R-CHOP and R-DHAP with ASCT may improve progression-free survival (PFS), failure-free survival (FFS), and duration of remission (DOR) compared with alternating R-CHOP and R-DHAP with ASCT (group A).

FMEC also considered input received from the Alberta Provincial Lymphoma Group, the Leukemia & Lymphoma Society of Canada Pharmacist Network, the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee (DAC), and the public drug programs to ensure there is alignment with unmet needs identified in the input.

FMEC concluded that ibrutinib demonstrates acceptable clinical value, and the reimbursement conditions were further developed based on significant unmet needs and economic considerations.

Therapeutic Landscape

What Is MCL?

MCL is a rare subtype of B-cell non-Hodgkin lymphoma (NHL) that develops from malignant B-lymphocytes within the outer region of a lymph node (i.e., mantle zone). MCL accounts for 5% to 10% of all new NHL diagnoses in Canada.

What Are the Current Treatment Options?

The current treatment approaches for first-line therapy (i.e., for patients who are treatment-naive) for MCL are primarily based on the patient's age, their suitability for intensive chemotherapy and potential ASCT, and the disease biology. Observation (known as the "watch and wait" strategy) is a suitable option for patients with asymptomatic MCL with a low tumour burden, leukemic non-nodal presentation, and nonbulky disease.

The standard of care in Canada for newly diagnosed younger (approximate age younger than 65 years) patients who are eligible for transplant consists of an alternating schedule of immunochemotherapy induction using R-CHOP and R-DHAP, followed by ASCT and 2 years of rituximab maintenance therapy. Some health care institutions administer bendamustine and rituximab (BR) for induction therapy before ASCT. In the relapsed and refractory setting, the current treatment options include Bruton tyrosine kinase (BTK) inhibitors, such as ibrutinib, and potentially CAR T-cell therapy, such as brexucabtagene autoleucel.

What Is the Treatment Under Review?

Ibrutinib is an oral drug that blocks BTK involved in cancer cell growth and survival in B-cell malignancies. Health Canada has approved ibrutinib for the treatment of adult patients with relapsed or refractory MCL, for whom the recommended dosage is 560 mg once daily. The requested nonsponsored reimbursement review is an off-label review of ibrutinib in combination with alternating R-CHOP and R-DHAP, with or without ASCT, for patients with MCL who have not previously received treatment and who are eligible for transplant.

Why Did We Conduct This Review?

At the request of clinicians, the participating public drug programs requested that we review ibrutinib in combination with immunochemotherapy with or without ASCT in patients with MCL who have not previously received treatment and who are eligible for transplant. Given the emerging clinical evidence of ibrutinib for untreated MCL, it may fulfill an unmet need to have more oral treatment options for patients who are unable to pursue intensive treatments (e.g., IV treatments, ASCT). The data protection for ibrutinib expired in 2023 and there are at least 4 generic drugs accepted and currently under review by Health Canada. Therefore, this ibrutinib treatment is eligible for a nonsponsored reimbursement review as per the Procedures for Reimbursement Reviews.

Input From Interested Parties

- Input submitted from the Alberta Provincial Lymphoma Group, the Leukemia & Lymphoma Society of Canada Pharmacist Network, and the Ontario Health (Cancer Care Ontario) Hematology Cancer DAC emphasized that not all patients with MCL achieve an adequate response to standard therapies, such as immunochemotherapy or ASCT. In addition, ASCT is an intensive therapy that requires prolonged hospitalization and carries risks of toxicities. These groups advocated for more effective and better-tolerated first-line treatments for MCL. Ideally, these options would provide durable response, reduce toxicity, improve survival, and promote health-related quality of life (HRQoL).
- **Public drug plans** inquired about the evidence for ibrutinib to inform a recommendation on whether ibrutinib in combination with immunochemotherapy with or without ASCT should be reimbursed in patients with MCL who have not previously received treatment and who are eligible for transplant. The public drug plans outlined implementation questions related to relevant comparators, initiation therapy, prescribing considerations, and economic issues.

► Refer to the main report and the supplemental material for this review.

Person With Lived Experience

A person with lived experience from Nova Scotia shared his 11-year treatment journey that included treatment with ibrutinib in the relapsed and refractory setting of MCL. After taking a “watch and wait” approach, treatment was initiated with alternating R-CHOP and R-DHAP, which was followed by ASCT. He shared that chemotherapy was debilitating. After experiencing a relapse in 2020, treatment was delayed due to COVID-19. Eventually, he started taking ibrutinib, which he continues to take. After 7 months of taking ibrutinib, a CT scan showed that his lymph nodes and spleen were normal with no trace of MCL. Seeing these results, he is more positive about his future. As an oral therapy, ibrutinib was easy to schedule and made everyday life much easier to plan. He shared that little effort is required on his part to manage his treatment plan. The medication is delivered to his door monthly, which is organized by the pharmacy. He emphasized the need for equitable access to this therapy, given its ease of use and effectiveness compared to other treatment options. He also emphasized that ibrutinib afforded him a better quality of life.

Disclaimer: The perspectives shared by people with lived experience who present to the committee reflect their individual experiences and are not necessarily representative of all people with the same condition or course of treatment. Their insights provide valuable context about what a patient, support person, or caregiver might go through when facing this condition or treatment, helping to inform the committee’s deliberations. These narratives complement other forms of evidence and input and should be considered as part of a broader understanding of the condition and treatment under review. Where gender or gendered pronouns are used in these narratives, they are included with the permission of the individual.

Summary of Deliberation

FMEC deliberated on all domains of value of the deliberative framework before developing their 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, please refer to the Expert Committee Deliberation at Canada's Drug Agency document.

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

Clinical Value

- FMEC concluded that ibrutinib demonstrates acceptable clinical value versus appropriate comparators in the Canadian setting.
- Through reflection on the insights shared by the person with lived experience, FMEC members noted the following important patient perspective: extending lifespan and improvement in quality of life are important. As noted by the person with lived experience, ibrutinib is an oral treatment that has the potential to avoid further hospital visits and exposure to infectious risks following treatment with immunochemotherapy and ASCT.
- FMEC members highlighted the following discussion points:
  - In the TRIANGLE trial, the comparators overall align with the current treatments recommended in Canada; the outcomes evaluated — including FFS, overall survival (OS), PFS, DOR, overall response rate (ORR) and complete response (CR) — are important for decision-making. FMEC noted that there is uncertainty with OS, as it was not reported and FFS has not been validated as a surrogate for OS.
  - FMEC noted that the effectiveness of ibrutinib is meaningful, with improvement in the primary outcome of FFS, which is driven by the reduction in progression of disease. The 3-year FFS for group A (representing the current standard of care) was 72% (95% confidence interval [CI], 67% to 79%), compared to group A + I (where ibrutinib was added to the current standard of care) was 88% (95% CI, 84% to 92%). The hazard ratio (HR) was 0.52 (1-sided 98.33% CI, 0 to 0.86).
- FMEC noted that, for the comparison of pooled ibrutinib-containing groups (group A + I and group I) to group A, CR and ORR improved in the pooled ibrutinib groups.
  - FMEC also noted that uncertainty remains regarding whether ibrutinib may displace treatment with ASCT, which is a key unmet clinical need in the treatment of MCL. FMEC heard from the guest specialists that there may be a shift to consider upfront treatment of ibrutinib based on this emerging evidence. In the TRIANGLE study, the comparisons between group A + I and group I (representing ibrutinib with immunochemotherapy without ASCT) were ongoing, and planned to be completed with prolonged follow-up at the end of the trial. As such, the question of whether ASCT can be deferred or delayed with the introduction of ibrutinib remains unknown at this time.
  - FMEC also discussed the relevant safety evidence. For the ibrutinib-containing groups, the safety results for group I suggested that treatment with ibrutinib only was better tolerated than ibrutinib

after ASCT (group A + I). In addition, hematological toxicity and infections occurred twice as frequently in the ibrutinib maintenance group treated with prior ASCT consolidation to the group with prior ASCT but without ibrutinib maintenance. FMEC also noted there are no data on long-term safety outcomes.

- FMEC noted that HRQoL is an important outcome, but there is a lack of data from the TRIANGLE trial to inform this important outcome. However, as noted by the person with lived experience, the option to treat with oral ibrutinib may help to avoid intensive treatment and travel requirements that are related to non-oral treatment options. Also, as noted by the guest specialists, ibrutinib may be beneficial to patients who live in rural communities because the administration of oral ibrutinib does not require travel to treatment centres that are usually located in urban areas.

Unmet Clinical Need

- FMEC concluded that there is a significant clinical need arising from MCL despite available treatments.
- Through reflection on the insights shared by the person with lived experience, FMEC members noted the following important patient perspective: more effective and better-tolerated first-line treatment options are needed for MCL.
- FMEC members highlighted the following discussion points:
  - MCL is a rare but aggressive form of NHL. The current standard of care for individuals who are diagnosed at an advanced stage (stage II to IV) includes treatment with intensive immunochemotherapy and ASCT. These are intensive treatment modalities that require significant time and resources. Further, there are additional monitoring requirements related to treatment toxicities. This is a source of significant unmet need for these patients, who prefer less invasive, less intensive, and equally effective treatment options.
  - While MCL is rare, there do not appear to be any major challenges in evidence generation given the availability of a phase III trial. Some FMEC members supported the allowance of greater uncertainty in the evidence due to the significant unmet need, citing possible rationales including the absence of curative therapy, older age at diagnosis, and high toxicity and adverse events associated with ASCT.

Distinct Social and Ethical Considerations

- FMEC concluded that ibrutinib would potentially address a significant nonclinical need arising from MCL despite available treatments.
- Through reflection on the insights shared by the person with lived experience, FMEC members noted the following important patient perspectives: oral ibrutinib may improve patient adherence to treatment and reduce the burden of frequent IV treatments. Patients may bear the cost of ibrutinib

directly in some jurisdictions, where funding of oral cancer treatment is variable and not always universal.

- **FMEC** members highlighted the following discussion points:
  - For patients eligible and requiring ASCT, this requires prolonged hospitalization and carries risks of severe adverse events, including myelosuppression, infections, organ injury, transplant-related mortality, and late secondary malignancies.
  - FMEC noted that, in MCL, the ongoing need for transplant (ASCT) requires acute care settings and specialized centres to deliver care and address complications. These treatment considerations add burdens to both patients and their caregivers.

Economic Considerations

- FMEC concluded that there are economic considerations that are important to address when implementing ibrutinib.
- **FMEC** members highlighted the following discussion points:
  - Based on publicly available prices, the reimbursement of ibrutinib for first-line treatment of previously untreated, transplant-eligible patients with MCL is expected to increase overall drug acquisition costs as it is an add-on therapy.
  - Ibrutinib in combination with alternating R-CHOP and R-DHAP likely demonstrates a clinical benefit compared with alternating R-CHOP and R-DHAP alone.
  - Given that ibrutinib is associated with increased drug acquisition costs and likely clinical benefit when added to R-CHOP and R-DHAP, price reductions may be required to ensure cost-effectiveness.
  - No evidence was identified regarding the cost-effectiveness of ibrutinib for the treatment of previously untreated, transplant-eligible patients with MCL. Therefore, estimates of cost-effectiveness were not available to the committee.
  - Ibrutinib is currently available as a brand name product in Canada, but at least 4 generic formulations are under review with Health Canada. If 1 generic product becomes available, the drug acquisition cost of ibrutinib for 28 days will drop to $2,782 when added to R-CHOP and R-DHAP. The price reduction will be greater if more than 1 generic product enters the market, as per the pan-Canadian Pharmaceutical Alliance (pCPA) tiered pricing framework.

Impacts on Health Systems

- FMEC did not identify any impacts on health systems that are important to address when implementing ibrutinib.
- FMEC members highlighted the following discussion points:

- Patients receiving ibrutinib in combination with immunochemotherapy may experience more toxicities. FMEC noted that more resources may be required to manage side effects, although the certainty around safety remains unknown due to incomplete safety reporting (e.g., any discontinuation related to treatment).
- FMEC also noted that it is uncertain if ibrutinib will alleviate the current challenges with health system sustainability, given the uncertainty on whether ASCT would be deferred or delayed with the addition of ibrutinib.
- FMEC also discussed the need for equitable access to all oral treatments for cancer.

Full Recommendation

With a vote of 7 to 0, FMEC recommends that ibrutinib in combination with immunochemotherapy with or without ASCT for previously untreated transplant-eligible adult patients with MCL be reimbursed, if the conditions presented in Table 1 are met.

Table 1: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Ibrutinib in combination with immunochemotherapy with or without ASCT may be initiated in adults for the treatment of MCL if all of the following conditions are met: 1.1. Adult patient with previously untreated MCL. 1.2. The patient is deemed transplant-eligible. 1.3. The patient has good performance status.	Based on findings from the TRIANGLE trial, ibrutinib plus alternating R-CHOP and R-DHAP with ASCT may improve PFS, FFS, and duration of remission compared with alternating R-CHOP and R-DHAP with ASCT. The initiation criteria are in alignment with TRIANGLE trial enrolment criteria. The TRIANGLE trial included patients with untreated, stage II to IV MCL.	Based on the TRIANGLE trial, the immunotherapy administered in combination with ibrutinib includes: • R-CHOP: IV rituximab 375 mg/m^2 on day 0 or 1, IV cyclophosphamide 750 mg/m^2 on day 1, IV doxorubicin 50 mg/m^2 on day 1, IV vincristine 1.4 mg/m^2 on day 1, and oral prednisone 100 mg on days 1 to 5 • R-DHAP (or R-DHAOx): IV rituximab 375 mg/m^2 on day 0 or 1, IV or oral dexamethasone 40 mg on days 1 to 3, IV cytarabine 2 doses of 2 g/m^2 for 3 hours every 12 hours on day 2, and IV cisplatin 100 mg/m^2 over 24 hours on day 1 (or alternatively, IV oxaliplatin 130 mg/m^2 on day 1) Note that in the TRIANGLE study, the maintenance dose of ibrutinib is 560 mg daily for a fixed duration of 2 years following immunochemotherapy and ASCT. Currently, there is a lack of evidence for combining ibrutinib with another immunochemotherapy regimen for this population.

Reimbursement condition	Reason	Implementation guidance
Discontinuation and renewal		
2. Ibrutinib should be discontinued if any of the following occur: 2.1. disease progression 2.2. unacceptable toxicities 2.3. completion of 2 years of maintenance ibrutinib following immunochemotherapy and ASCT, whichever occurs first.	Consistent with clinical practice, patients in the TRIANGLE study discontinued treatment upon disease progression and unacceptable toxicities.	—
Prescribing		
3. Prescribing should be limited to clinicians with expertise in the diagnosis and management of MCL.	This will ensure that treatment is prescribed for appropriate patients and adverse events are optimally managed.	—
Pricing		
4. A price reduction may be required.	The reimbursement of ibrutinib in combination with immunochemotherapy with or without ASCT for previously untreated, transplant-eligible patients with MCL is expected to increase overall drug acquisition costs, as it is an add-on therapy to other regimens. No evidence was identified regarding the cost-effectiveness of ibrutinib. Therefore, estimates of cost-effectiveness were not available to the committee. A cost-effectiveness analysis would be needed to determine whether ibrutinib is cost-effective. Given that ibrutinib is associated with increased drug acquisition costs and likely clinical benefit when added to R-CHOP and R-DHAP, price reductions may be required.	—

ASCT = autologous stem cell transplant; FFS = failure-free survival, MCL = mantle cell lymphoma; PFS = progression-free survival; R-CHOP = rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone, R-DHAOx = rituximab, dexamethasone, cytarabine, and oxaliplatin; R-DHAP = rituximab, dexamethasone, cytarabine, and cisplatin.

Feedback on Draft Recommendation

CDA-AMC received feedback from 1 clinician group (the Ontario Health [Cancer Care Ontario] Hematology Cancer DAC), 1 patient group (the Leukemia & Lymphoma Society of Canada), and the public drug programs. The public drug programs requested a minor editorial revision to clarify that ibrutinib may be discontinued following the maintenance treatment period of 2 years. The clinician group also suggested revising the wording of the treatment duration of ibrutinib to reflect an accumulated 2 years of maintenance therapy, and shared other considerations relevant to the treatment of MCL.

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

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Zaina Albalawi, Dr. Hardit Khuman, Ms. Valerie McDonald, Dr. Bill Semchuk, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, and Dr. Dominika Wranik. Two guest specialists from Ontario and the Prairies participated in this review.

Meeting date: September 18, 2025

Regrets: One expert committee member did not attend the meeting.

Conflicts of interest: None

Special thanks: CDA-AMC extends our special thanks to Fred Devlin, who presented directly to FMEC on behalf of people with lived experience, and the patient organizations representing the community of those living with MCL, particularly the Leukemia & Lymphoma Society of Canada.

Note: CDA-AMC makes every attempt to engage with people with lived experience as close to the indication and treatments under review as possible; however, at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys or experience with comparators under review to ensure lived experience perspectives are included and considered in Reimbursement Reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journeys with FMEC.

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