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Reimbursement Recommendation

Blinatumomab

Reimbursement request: In combination with a tyrosine kinase inhibitor for the first-line treatment of Philadelphia chromosome positive acute lymphoblastic leukemia in adult and pediatric patients

Requester: Public drug programs

Final recommendation: Do not reimburse

Summary

What Is the Reimbursement Recommendation for Blinatumomab?

The Formulary Management Expert Committee (FMEC) recommends that blinatumomab in combination with a tyrosine kinase inhibitor (TKI) not be reimbursed for the first-line treatment of adult and pediatric patients with Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia (ALL).

Why Did Canada's Drug Agency Make This Recommendation?

FMEC reviewed 3 single-arm, open-label phase II trials (GIMEMA LAL2116 D-ALBA, SWOG-1318, and MDACC) in adult patients with Ph-positive ALL, as well as a cost comparison of blinatumomab versus other treatments used in Canada. There was no direct or indirect clinical evidence available that compared blinatumomab with a relevant comparator (e.g., standard of care chemotherapy) as first-line treatment for adult patients with Ph-positive ALL and no evidence that met the inclusion criteria for the pediatric population.

Patients and clinicians identified a need for first-line treatments that prolong disease remission and survival, reduce toxicities, and maintain health-related quality of life (HRQoL). FMEC agreed that the use of blinatumomab in combination with a TKI may potentially avoid the use of high-dose chemotherapy with or without an allogeneic stem cell transplant (allo-SCT), which are highly toxic. However, based on the available evidence, FMEC concluded that there was significant uncertainty in the clinical value demonstrated by blinatumomab in combination with a TKI due to the limitations of the available evidence (e.g., lack of formal hypothesis testing, small sample size, missing information, and indirectness of the population). The committee recognized that patients want longer survival, less toxicity, and improved HRQoL. However, without direct evidence, FMEC concluded it is uncertain whether blinatumomab in combination with a TKI addresses these significant unmet clinical and nonclinical needs.

Review Background

What Is Ph-Positive ALL?

Ph-positive ALL is a cancer in the stem cells of the blood caused by a genetic mutation. Diagnoses of Ph-positive ALL increase with age. Symptoms can include fatigue, dyspnea, fever, night sweats, and easy bruising or bleeding. In children, pain in the extremities or joints may be the only presenting symptom. It was estimated that 440 adults in Canada were newly diagnosed with ALL in 2019. The 5-year overall survival rate for adults with Ph-positive ALL is approximately 25%.

What Are the Current Treatment Options?

The first-line treatment of Ph-positive ALL includes pediatric or pediatric-inspired multidrug regimens that combine chemotherapy with a TKI.

What Is the Treatment Under Review?

Blinatumomab is a bispecific T-cell engager molecule that binds to CD19 surface antigens of B cells and CD3 antigens of T cells to induce apoptosis in malignant B cells. Blinatumomab is available as a 38.5 mcg per vial powder for IV infusion. Blinatumomab has been approved by Health Canada for the treatment of:

- patients with Ph-negative CD19-positive B-cell precursor ALL in the consolidation phase of multiphase chemotherapy
- patients with Ph-negative CD19-positive B-cell precursor ALL in first or second hematologic complete remission with minimal residual disease (MRD) greater than or equal to 0.1%
- adult patients with relapsed or refractory B-cell precursor ALL
- pediatric patients with Ph-negative relapsed or refractory B-cell precursor ALL.

The use of blinatumomab in combination with a TKI for the first-line treatment of Ph-positive ALL in adult and pediatric patients is considered off label.

Why Did We Conduct This Review?

The participating public drug programs requested a review of blinatumomab in combination with a TKI for the first-line treatment of adult patients with Ph-positive ALL. After the review was initiated, the public drug plans, informed by input from a provincial pediatric oncology group, requested that the scope be expanded to include pediatric patients. There is emerging evidence for the use of blinatumomab in the first-line setting, and blinatumomab is also viewed by clinicians as a less toxic treatment option than existing therapies. Data protection for blinatumomab ended on June 22, 2024, making it eligible for a non-sponsored reimbursement review per the Procedures for Reimbursement Reviews.

Highlights of Input From Interested Parties

- One patient group, **Leukemia & Lymphoma Society of Canada**, highlighted that important treatment goals for patients with ALL and their caregivers include prolonging disease remission while minimizing toxicity and maintaining HRQoL.
- Three clinician groups, the **Canadian Leukemia Study Group – Groupe Canadienne d'Étude sur la Leucémie**, the **Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee**, and the **Pediatric Oncology Group of Ontario**, advocated for patients with Ph-positive ALL to have access to first-line treatments that enable deep molecular remission, prolong survival, and reduce the risk of relapse and the need for subsequent therapies.
- **Public drug plans** inquired about the evidence for blinatumomab to inform a recommendation for whether it should be reimbursed in combination with a TKI as a first-line treatment for Ph-positive ALL in adult and pediatric patients. The public drug plans outlined implementation questions related to treatment comparators, treatment eligibility, prescribing, generalizability, and care provisions.

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

Person With Lived Experience

A woman living rurally in central Canada shared her journey with Ph-positive ALL and related treatment. A visit to her family doctor and blood work in 2014 to investigate some extreme fatigue she had been feeling confirmed she had leukemia. She was shocked and devastated by the news. She travelled to an urban care centre within the province to begin chemotherapy immediately. She was admitted and spent close to 5 months in the hospital. Her treatment included imatinib; 2 courses of hypercyclophosphamide, vincristine sulphate, doxorubicin hydrochloride (Adriamycin), and dexamethasone (CVAD) A and B; neupogen injections; a stem cell transplant; and immunosuppressant drugs (sirolimus and tacrolimus). The extended separation from her husband and teenage children was profoundly difficult for her. Despite visits and a period of temporary relocation for her family to be close to her, she acutely felt the loss of her daily functioning as a partner and parent. Upon discharge, she struggled to reintegrate into life as she had previously known it. Cancer had changed her family dynamic. Post-transplant, she developed chronic graft-versus-host disease and has experienced ongoing issues with her eyes, ears, skin, and joints. She is on continuous oxygen because of damage to her lungs resulting from treatment complications. Medication costs over the years have been high and she pays for the majority out of pocket. Her family, friends, and community are a great source of support to her, and she faces each new day with hope, positivity, and resilience.

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. When gender or gendered pronouns are used in these narratives, they are included with the permission of the individual.

Recommendation

With a vote of 9 to 0, FMEC does **not** recommend that blinatumomab with a TKI for the treatment of Ph-positive ALL in adult or pediatric patients be reimbursed by publicly funded drug plans.

Summary of Deliberation

FMEC deliberated on 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, please refer to Expert Committee Deliberation at Canada's Drug Agency.

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

Clinical Value

- **FMEC concluded that it is uncertain whether blinatumomab with a TKI demonstrates acceptable clinical value versus appropriate comparators in the Canadian setting.**
- Through reflection on the input from a patient group or insights shared by people with lived experience, FMEC members noted the following important patient values or perspectives: when making decisions about new treatment options for ALL, patients consider quality of life during treatment, predicted number and severity of side effects, and financial costs. Both patients and caregivers value longer remission time, extending life, and less treatment toxicity.
- **FMEC** members highlighted the following discussion points:
  - **Efficacy compared to appropriate comparators:** Current standard of care for patients with Ph-positive B-cell precursor ALL is induction treatment with chemotherapy plus a TKI (i.e., imatinib, dasatinib, or ponatinib), consolidation treatment, and maintenance treatment.
  - FMEC reviewed 3 phase II noncomparative studies using blinatumomab in the consolidation or postremission phases for adult patients with newly diagnosed Ph-positive ALL. One study used blinatumomab with ponatinib in the induction phase. FMEC noted that there is no direct comparison to any standard therapies used for Ph-positive ALL.
  - There was also no indirect evidence available for FMEC to review. The guest specialists shared their opinion that blinatumomab therapy is superior to standard of care therapies based on evidence of efficacy in the relapsed or refractory Ph-negative ALL adult population.
  - FMEC heard from the guest specialists that blinatumomab activity should not differ between Ph-positive and Ph-negative B-cell ALL based on the mechanism of action. Historically, both groups

were treated similarly but treatment for each diverged over time. Blinatumomab was added to treatment protocols for Ph-negative B-cell ALL to potentially omit subsequent chemotherapy, steroids, and transplant. The guest specialists felt that blinatumomab in Ph-positive ALL might offer the same benefit of avoiding more toxic therapies.

- **Outcomes assessed:** The committee agreed that the outcomes assessed (i.e., disease-free survival, overall survival, event-free survival, MRD, and toxicity) were important to patients; however, no HRQoL outcomes were assessed. The guest specialists shared with FMEC that MRD is a validated outcome with increased sensitivity of newer assays and is highly predictive of relapse in ALL.
- **Harms:** The committee heard from the patient with lived experience about the toxicities she has had and continues to have because of high-dose chemotherapy and stem cell transplant. FMEC agreed that the use of blinatumomab in combination with a TKI can potentially avoid the use of high-dose chemotherapy with or without an allo-SCT, which are highly toxic.
- Blinatumomab-associated adverse events could include cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, which necessitate intensive care unit support and inpatient delivery of treatment for the initial few days of the first, and potentially second, cycle of blinatumomab.
- **Level of certainty in clinical value**: The committee agreed that although most short-term survival outcomes and molecular remission in the noncomparative studies were potentially a signal of efficacy, the results were uncertain or very uncertain based on risk of bias and imprecision. FMEC discussed the limitations of the internal validity of the evidence (e.g., small sample sizes, lack of formal hypothesis testing and outcome measurement, and missing information).
- Canada's Drug Agency (CDA-AMC) did not identify any studies that included the pediatric patient population. FMEC was unable to assess the clinical value of the drug for pediatric patients with Ph-positive ALL due to the gap in available evidence. FMEC noted that blinatumomab has been approved for pediatric patients with Ph-negative CD19-positive B-cell precursor ALL for consolidation for up to 2 cycles, and after first or second clinical response for pediatric patients with MRD-positive disease. Blinatumomab has improved survival and decreased relapse in these settings. While neither of the guest specialists treat pediatric patients, both stated that the clinical benefit of blinatumomab in pediatric patients with Ph-negative ALL support its use in pediatric patients with Ph-positive disease.
- **Evidence generation:** The committee acknowledged that Ph-positive ALL is a rare illness. Most evidence for treatment with blinatumomab comes from phase I or II trials, but there are ongoing phase III trials in both the adult and pediatric populations. Specifically, there are 2 ongoing phase III trials in adults comparing blinatumomab in combination with a TKI with chemotherapy plus a TKI that have estimated completion dates in 2027 and 2028. The preliminary results for 1 of these trials are expected later this year. There is 1 ongoing phase III trial in pediatric patients studying chemotherapy plus a TKI with blinatumomab that will finish accrual in 2030.

Unmet Clinical Need

- **FMEC concluded that there is a significant clinical need arising from Ph-positive ALL despite available treatments; however, it is uncertain if blinatumomab with a TKI addresses this need.**
- Through reflection on the input from the patient group and insights shared by people with lived experience, FMEC members noted the following important patient value and perspective: ALL negatively impacts the lives of patients. There are also challenges related to the burden of illness, such as emotional distress, changes in living arrangements, disruption of daily routines, and caregiving needs during the treatment period. The social lives of patients are also affected (e.g., isolation [due to immunosuppression], loss of friendships and social engagement [due to fatigue and physical limitations], and emotional withdrawal [due to appearance or confidence changes]). Patients report severe adverse events, including infections, fatigue, and neutropenia. Similarly, the patient with lived experience recounted infections in the lungs and skin leading to sepsis, and highlighted experiencing daily fatigue.
- **FMEC** members highlighted the following discussion points:
  - **Availability of treatment options:** The committee agreed that alternative treatments include high-dose multidrug chemotherapy with a TKI with or without an allo-SCT. Despite the available treatment options, there continue to be unmet needs (e.g., improvement in survival outcomes, less toxicity, reduced dependence on transplants, and minimized monitoring for short-term and long-term complications).
  - **Severity of the disease:** FMEC agreed that ALL is a severe disease with long-term treatment protocols and maintenance therapy for up to 5 years. The disease has a high risk of central nervous system relapse and significant death rates.
  - **Significant unmet clinical need:** The committee recognized that patients want increased length of life, less toxicity, and improved HRQoL.
  - FMEC heard from the guest specialists that blinatumomab protocols have the potential to reduce the need for chemotherapy and an allo-SCT. Although there were no formal HRQoL results reported, HRQoL could be improved with treatment potentially closer to home and less toxic high-dose chemotherapy.

Distinct Social and Ethical Considerations

- **FMEC concluded that it is uncertain whether blinatumomab with a TKI would address a significant nonclinical need arising from Ph-positive ALL despite available treatments.**
- **FMEC did not identify any important measures that should be implemented to ensure the use of blinatumomab with a TKI addresses relevant social and ethical implications.**
- Through reflection on the input from the patient groups and insights shared by people with lived experience, FMEC members noted that treatment for Ph-positive ALL requires prolonged and difficult stays in hospital (i.e., away from home). When patients are surrounded by family in the home, they

heal quicker both physically and emotionally. Therefore, treatments that can be received while staying closer to home are needed.

- **FMEC** members highlighted the following discussion points:
  - **Unmet nonclinical needs:** FMEC recognized that the standard of care treatment requires long inpatient admission for weeks of treatment while blinatumomab may be able to be delivered mainly as an outpatient option if 24-hour pumps and nursing and/or pharmacy care are available for the 28-day infusion. This may allow for treatment closer to home.
  - The committee stated that patients would like to be treated closer to home and not have to upend their lives to live closer to tertiary treatment centres. The need for more hematologists or clinicians to manage blinatumomab in the community remains.
  - There is also a need for molecular testing to determine molecular response. The guest specialists stated that reverse transcription polymerase chain reaction testing is available in all provinces, while next-generation sequencing is not and is not commonly used outside of the research setting.
  - **Social or ethical considerations:** Patients who live a long distance from a leukemia treatment centre need to receive the same level of care as those who live near large centres. Patents' caregivers need training to manage blinatumomab outpatient infusion.
  - FMEC heard from the guest specialists that blinatumomab treatment is not currently being moved to the community as it is logistically difficult to give continuous IV infusion. However, patients can spend less time in a tertiary care hospital. Although not currently available, a clinical trial on subcutaneous administration of blinatumomab for ALL is under way.

Economic Considerations

- **FMEC reviewed the economic considerations for blinatumomab in combination with a TKI. Given that blinatumomab was not recommended for reimbursement based on unacceptable clinical value and failure to address a significant unmet need, further deliberation on economic considerations was not required.**

Impacts on Health Systems

- **FMEC considered the impacts on health systems when implementing blinatumomab in combination with a TKI. Given that blinatumomab was not recommended for reimbursement based on unacceptable clinical value and failure to address a significant unmet need, further deliberation on measures to address these impacts was not required.**

Sources of Information Used by the Committee

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

- the CDA-AMC review of the clinical and pharmacoeconomic evidence related to blinatumomab (refer to the Main Report and the Supplemental Material document)
- patients' perspectives gathered by 1 patient group, the Leukemia & Lymphoma Society of Canada
- input from a person with lived experience who delivered a brief presentation and answered questions from the committee (refer to the Person With Lived Experience section in this document)
- input from 3 clinician groups, the Canadian Leukemia Study Group – Groupe Canadienne d'Étude sur la Leucémie, the Pediatric Oncology Group of Ontario, and the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
- input from the public drug programs that participate in the reimbursement review process
- input from 2 guest specialists with expertise in the management of adult ALL who were consulted by CDA-AMC.

Feedback on Draft Recommendation

CDA-AMC received feedback from 1 patient group (the Leukemia & Lymphoma Society of Canada), 3 clinician groups (the Canadian Leukemia Study Group – Groupe Canadienne d'Étude sur la Leucémie, the Ontario Health [Cancer Care Ontario] Hematology Cancer Drug Advisory Committee, and the Pediatric Oncology Group of Ontario), the drug manufacturer (Amgen Canada), and the public drug programs. Based on feedback from the patient group, clinician groups, and drug manufacturer, editorial revisions were made to provide clarity on the committee's deliberations. Feedback was received that the results from the GIMEMA ALL2820 trial were not included in the systematic review of the clinical evidence. At the time of the literature search, there was no full publication available and conference abstracts do not meet the review eligibility criteria. A resubmission based on new clinical information that addresses specific issues identified by FMEC in the final recommendation, from either the participating drug programs if this new evidence is published (Oncology Working Group) or the drug manufacturer (Amgen Canada), could be considered in the future.

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, Ms. Marilyn Barrett, Dr. Hardit Khuman, Ms. Valerie McDonald, Dr. Bill Semchuk, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik. Two guest specialists from Atlantic Canada and Ontario participated in this review.

Meeting date: January 22, 2026

Conflicts of interest: None

Special thanks: CDA-AMC extends special thanks to the individuals who presented directly to FMEC and to patient organizations representing and supporting the community of people living with leukemia, including Colleen McMillan, Terri Lynn Hall, and the Leukemia & Lymphoma Society of Canada.

Note: CDA-AMC makes every attempt to engage with people with lived experience as closely 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 the 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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