DRAFT Reimbursement Recommendation

Blinatumomab

> Reimbursement request: **For pediatric patients with Philadelphia chromosome negative relapsed/refractory B precursor acute lymphoblastic leukemia (ALL) who are in first relapse.**
>
> Requester: Public drug programs
>
> Draft Recommendation: Reimburse with conditions

Summary of Recommendation

The Formulary Management Expert Committee (FMEC) recommends that blinatumomab for the treatment of pediatric Philadelphia-negative B-cell acute lymphoblastic leukemia (B-ALL) at first relapse, be reimbursed provided certain conditions are met.

FMEC reviewed evidence from two trials, identified by CDA-AMC's systematic review of the literature: Locatelli et al. (2021), which compared blinatumomab to multi-drug chemotherapy in pediatric patients with high-risk first relapse Ph-negative B-ALL; and COG AALL1331, which compared blinatumomab to multi-drug chemotherapy in patients aged 1 to 30 years with low-, intermediate-, or high-risk first relapse Ph-negative B-ALL. FMEC also considered input received from external partners, including Leukemia & Lymphoma Society of Canada, Advocacy for Canadian Childhood Oncology Research Network, Ontario Parents Advocating for Children with Cancer, and Childhood Cancer Canada, the Pediatric Oncology Group of Ontario (POGO), Amgen Canada and public drug programs.

FMEC concluded that for intermediate- and high-risk first relapse patients, blinatumomab may offer clinically meaningful benefits in event-free survival, disease-free survival, overall survival, minimal residual disease remission and progression to transplant compared to standard chemotherapy. In addition, blinatumomab is associated with lower toxicity and may offer meaningful nonclinical benefits, including the potential for at-home administration.

FMEC also concluded that for low risk first relapse patients, there is uncertain evidence of benefit in disease-free survival and overall survival. However, blinatumomab is associated with lower toxicity and may offer meaningful nonclinical benefits, including the potential for at-home administration.

The expected cost of blinatumomab is higher than that of chemotherapy based on publicly available list prices. FMEC discussed the importance of considering the increased drug cost in the context of other economic impacts, including the management of toxicity-related adverse events (AEs) and changes in patient outcomes. A full cost-effectiveness analysis would be required to assess this overall impact.

Therapeutic Landscape

What Is Pediatric Philadelphia-negative B-cell Acute Lymphoblastic Leukemia (Ph-negative B-ALL)?

ALL is a common childhood cancer with Ph-negative B-ALL being the most common subtype. It originates from immature B-lymphocytes and disrupts normal blood production in the bone marrow, leading to symptoms like fatigue, recurrent infections, bruising and bleeding. Around 10 to 15% of patients experience relapse, with poor prognosis and a 5-year overall survival rates ranging from 35-50%.

What Are The Current Treatment Options?

In relapsed ALL, the main treatment goals are to prolong time to next relapse, improving overall survival, achieving a deep molecular response, and enabling high-risk patients to proceed to hematopoietic stem cell transplantation (HSCT), while managing or limiting serious adverse effects.

Currently in Canada, treatment for first relapse involves reinduction therapy to achieve a second complete remission followed by consolidation therapy. Consolidation therapy options include multi-agent chemotherapy, immunotherapy where available and / or possibly HSCT for high-risk patients.

Why Did We Conduct This Review?

In most jurisdictions, pediatric patients with Ph-negative B-ALL at first relapse are currently treated with chemotherapy; however, some jurisdictions also fund blinatumomab following any relapse. There is emerging evidence for the use of blinatumomab in the setting of first relapse and blinatumomab is also viewed as being a less toxic treatment option for these patients. Blinatumomab was eligible for a nonsponsored reimbursement review given that the data protection period for blinatumomab has expired. At the request of publicly funded drug plans, we reviewed the available evidence on the efficacy and safety of blinatumomab in the treatment of pediatric patients with Ph-negative B-ALL at first relapse.

Input from Partners

- **Four patient groups**, **Leukemia & Lymphoma Society of Canada**, **Advocacy for Canadian Childhood Oncology Research Network**, **Ontario Parents Advocating for Children with Cancer**, and **Childhood Cancer Canada**, jointly submitted input for this review. Their input highlighted the profound physical, emotional, and financial impacts that pediatric cancer relapse has on both patients and their families. They emphasized the need for treatments that are innovative, effective, convenient and have minimal side effects.
- **The Pediatric Oncology Group of Ontario (POGO)** provided input and noted the growing evidence supporting the use of blinatumomab in earlier settings of Ph-negative B-ALL in pediatric patients. They highlighted that consolidation therapy for patients at first relapse traditionally involves 3 intensive chemotherapy blocks, which requires hospitalization due to toxicity risks.
- **Amgen Canada Inc**, a manufacturer for blinatumomab, submitted input in supporting this review.
- **Public drug plans** inquired about whether the evidence for blinatumomab for pediatric patients with Ph-negative B-ALL at first relapse supports reimbursement. The public drug plans outlined implementation questions related to treatment eligibility and potential costs.

Refer to the main report and working papers for this review.

Person With Lived Experience

A mother presented her family's journey with acute lymphoblastic leukemia. Her daughter was diagnosed at Christmas in 2018 and underwent intensive chemotherapy, achieving remission in 2021. She relapsed a year later, leading her family to pursue blinatumomab after exhausting other options. Initially denied coverage, the hospital eventually secured the treatment. She shared how blinatumomab, administered at home, was life-changing, with fewer side effects than chemotherapy and allowed her daughter to regain her energy and emotional well-being. Despite the logistical challenges of home infusions—such as frequent IV pump alarms and long drives for equipment changes, she emphasized the transformative impact of blinatumomab on her daughter's quality of life and the significant impact on their family dynamic.

Deliberation

The committee deliberated on the following 5 domains of value:

- **Clinical Value:** The value that patients derive from a health technology in terms of its effect on their health and health-related quality of life. The determination of the clinical value of a health technology requires the measurement of its clinical benefits and harms and an assessment of the impact of these effects on patients. Clinical benefits and harms are assessed against relevant comparators.
- **Unmet Clinical Need:** Morbidity and/or mortality arising from a condition or symptom that is not addressed effectively by available treatments.
- **Distinct Social and Ethical Considerations:** The social and ethical implications of health technologies not already assessed in the other domains and how they affect patients, caregivers, populations, and the organization of health systems. This includes non-clinical needs—social, psychological, and logistical factors affecting the appropriateness, accessibility, and acceptability of the technology beyond its direct clinical outcomes—as well as broader ethical considerations in the design, evaluation, and implementation of these technologies.
- **Economic Considerations:** Economic evidence to inform the financial, human or other resource implications associated with the technology under review, and whether it is worthwhile to allocate resources to the technology under review given its expected clinical benefits. Considerations may include the potential resource or cost impacts of the technology under review versus relevant comparator(s).
- **Impacts on Health Systems:** Two distinct but interrelated components: organizational feasibility of adoption is the ease with which the health technology can be implemented in the health system while realizing its clinical value, while economic feasibility of adoption examines how the adoption of a health technology will economically impact the payer or budget holder.

Decision Summary

Table 1: Summary of Deliberation

Domain	Discussion point(s)
Clinical Value	• **FMEC noted that blinatumomab demonstrate uncertain clinical value versus relevant comparators. The clinical value of blinatumomab differs based on risk group.** • FMEC discussed the clinical value of blinatumomab based on different risk groups: **Low Risk for First Relapse:** ○ Based on the results of the COG ALL 1331 published by Hogan et al. (2023), no significant different was observed between blinatumomab and chemotherapy in disease free survival (61.2% ± 5.0% for chemotherapy with blinatumomab vs 49.5%±5.2% for chemotherapy alone) or overall survival (90.4% ± 3.0% for with blinatumomab vs 79.6%±4.3% for chemotherapy alone). ○ FMEC discussed the limitations (e.g., lack of power) associated with the post-hoc analysis of the COG AALL 1331 trial looking at potential disease site subgroups based on bone marrow involvement. **High Risk or Intermediate Risk for First Relapse** ○ Based on the results of the COG ALL 1331 trial published by Brown et al.(2021), a 2-year disease free survival was 54.4% for blinatumomab versus 39.0% for chemotherapy, with HR for disease progression or mortality of 0.70, 95% CI, 0.47 to 1.03, 1 sided p =0.03. ○ FMEC noted that interpretation is challenging due to early cessation of randomization and potential for an underpowered primary endpoint **High Risk for First Relapse:** ○ Based on the results of Locatelli et al (2021) which evaluated event-free survival in children with high risk first relapse B-ALL after a consolidation course with blinatumomab vs consolidation chemotherapy before allogeneic hematopoietic stem cell transplant, the incidence of events for event-free survival in the blinatumomab vs consolidation chemotherapy group was 31% vs 57% (HR 0.33, 95% CI 0.18-0.61). Overall survival HR 0.43 (95% CI 0.18-1.01). Minimal residual disease remission was more frequent in the blinatumomab vs consolidation chemotherapy group (90% vs 54%; difference 35.6% (95% CI, 15.6%-52.5%)). ○ FMEC noted that the clinical value appeared to be most notable in the high risk group, although uncertainty in the evidence remained. • FMEC noted across both the COG ALL 1331 and Locatelli trial that blinatumomab was associated with significantly lower rates of severe toxicity than chemotherapy including febrile neutropenia, infections, sepsis, anemia and mucositis.
Unmet Clinical Need	• **FMEC concluded that overall, there is a clinical unmet need for patients with Philadelphia chromosome negative B-ALL who are in first relapse, however, there is uncertainty in the unmet clinical need based on risk groups.** • FMEC noted that there is a significant clinical need for pediatric patients with Philadelphia chromosome negative B-ALL who are in first relapse. Despite high chance of cure with initial intensive chemotherapy with or without allogeneic stem cell transplant, 10 to 15% of patients relapse. The historical 5-year survival rates for children, adolescents and young adults with first relapse is 35 to 50%.

	• FMEC also noted that, due to the significant adverse effects of chemotherapy or inability to achieve minimal residual disease-negative second remission through chemotherapy, many patients with early relapse are not candidates for treatment with transplant. • Blinatumomab demonstrated less toxicity in the ALL population compared to conventional chemotherapy. The guest clinical specialists highlighted that the improved safety profile of blinatumomab, in their experience, translates to less transfusion required (e.g. for hematological toxicities) and less hospitalization required (e.g., for potential infectious complications). • FMEC also discussed other benefits with blinatumomab, such as the ability to administer this medication at home. However, it was also noted that caregivers may need support to manage the administration of blinatumomab at home (e.g., trouble-shooting with blockage of the intravenous line).
Distinct Social and Ethical Considerations	• **As heard from the patient with lived experience, despite available treatments FMEC concluded that there is significant non-clinical need[1] arising from the condition that would potentially be addressed by blinatumomab.** • FMEC also noted that currently, there is a lack of consistent access of blinatumomab treatment in cancer centers from different jurisdictions. Additionally, the high cost of treatment can be a burden for patients and families. • FMEC discussed that while ALL predominantly affects white individuals, the 2 trials, which were largely composed of white participants, did not include representation from diverse populations. • FMEC discussed that blinatumomab may offer social benefits for pediatric patients by enabling the possibility of treatment at home, allowing patients to spend quality time with their families rather than remaining in hospital. Additionally, by avoiding chemotherapy and its associated side effects (e.g., fatigue, hematological side effects, or infections), patients may be well enough to attend school, participate in other social activities, and achieve important developmental milestones. • Patients with Down syndrome, Ph +, prior HSCT or prior blinatumomab were excluded from trial and, as such, little information is available to guide decision making in this population
Economic Considerations	• FMEC discussed that drug costs of blinatumomab are higher than those of chemotherapy. A cost-effectiveness analysis was not available to inform pricing conditions. FMEC discussed the need to consider the increased drug cost within the context of the economic impact of reduced toxicity-related AEs and improved patient outcomes.
Impacts on Health Systems	• FMEC noted blinatumomab is currently utilized in other indications and populations. There are no specific concerns with implementing treatment option for this population. It appears that management of infusions are occurring in other scenarios and can occur through current infrastructure. Bag changes could occur outside of specialized pediatric cancer centers provided appropriate training occurs for families or other at-home caregivers.

AE = adverse events; ALL = acute lymphoblastic leukemia; B-ALL = B-cell precursor acute lymphoblastic leukemia; CI = confidence interval; CNS = central nervous system; HR = hazard ratio; FMEC = Formulary Management Expert Committee; HSCT = hematopoietic stem cell transplantation; Ph + = Philadelphia positive

[1] Non-clinical need" refers to the social, psychological, and logistical factors that influence the appropriateness, accessibility, and acceptability of a health technology beyond its direct clinical outcomes. This includes the perspectives and experiences of patients, caregivers, and providers regarding the condition and the expected outcomes of the treatment, as well as considerations of the care setting (e.g., home, community, or hospital), geographic factors (e.g., distribution of services and travel requirements), treatment burden on patients, family, and caregivers, mode of administration, and referral or prescriber requirements.

Full Recommendation

With a vote of 8 to 0, the FMEC recommends that blinatumomab be reimbursed for pediatric patients with Philadelphia chromosome negative relapse or refractory B precursor acute lymphoblastic leukemia (ALL) who are in first relapse if the conditions presented in Table 2 are met.

Table 2: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Blinatumomab should be reimbursed if the following conditions are met: 1.1. Aged 1 to 18 years old 1.2. Philadelphia chromosome negative B-cell precursor ALL (B-ALL) in first relapse	Based on evidence from COG ALL 1331 and study by Locatelli et al. (2021) for the age group as requested by the public drug programs.	Although blinatumomab is associated with neurotoxicity and may pose an increased risk for patients with pre-existing CNS pathology and CNS ALL involvement, there may be patients with CNS ALL involvement who may benefit from blinatumomab, such as those with combined systemic and bone marrow disease. However, the clinical experts recommended against using blinatumomab in the case of isolated CNS disease, given its poor blood-brain barrier penetration.
Discontinuation		
2. Blinatumomab should be discontinued if there is: 2.1. Disease progression 2.2. Intolerable adverse events	Consistent with clinical practice and patients enrolled in the COG ALL 1331 and Locatelli et al (2021) studies	-
Prescribing		
3. Prescribing should be limited to clinicians with expertise in the diagnosis and management of acute lymphoblastic leukemia.	This will ensure that treatment is prescribed for appropriate patients, and adverse events are optimally managed.	-
Cost		
4. A price reduction may be required.	Based on publicly available prices, blinatumomab is more costly than chemotherapy in pediatric patients with Ph-negative relapsed or refractory B-ALL. A price reduction may be therefore required. A cost-	-

Reimbursement condition	Reason	Implementation guidance
	effectiveness analysis would be needed to determine the extent of a desirable price reduction.	

Abbreviation: ALL = acute lymphoblastic leukemia; B-ALL = B-cell precursor acute lymphoblastic leukemia; CNS = central nervous system

Feedback on Draft Recommendation

<to be updated after the feedback period>

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, Dr. Dominika Wranik, as well as two guest specialists from British Columbia and Ontario.

Meeting date: November 21, 2024

Conflicts of interest: None

Special thanks: CDA-AMC extends our special thanks to the individuals who presented directly to FMEC on behalf of patients with lived experience and to patient organizations representing the community of those living with ALL, including the Leukemia & Lymphoma Society of Canada, which includes Colleen McMillan, Mellissa Patrick and Christina Sit.

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 use 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 journey with the FMEC committee.

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

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