Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient/Clinician/Industry Input

blinatumomab

(non-sponsored review)

Indication: Indicated for the pediatric patients with Philadelphia chromosome negative relapsed/refractory B precursor acute lymphoblastic leukemia (ALL) who are in first relapse.

Jan 3, 2025

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

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CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: blinatumomab (Blincyto)
Indication: Indicated for the pediatric patients with Philadelphia chromosome negative relapsed/refractory B precursor acute lymphoblastic leukemia (ALL) who are in first relapse.
Name of Patient Group: The Leukemia & Lymphoma Society of Canada (LLSC)
Author of Submission: Colleen McMillan, Advocacy Lead, LLSC

1. About Your Patient Group

The Leukemia & Lymphoma Society of Canada - bloodcancers.ca
LLSC is a national charitable status organization dedicated to finding a cure for blood cancers and its ability to improve the quality of life of people affected by blood cancers and their families by funding life-enhancing research and providing educational resources, services, and support. The Leukemia and Lymphoma Society of Canada is the largest charitable organization in Canada dedicated to blood cancer, our focus includes:

- Funding research from bench to bedside.
- Rethinking how a person navigates their blood cancer experience
- Providing targeted blood cancer information
- Offering tools for psychological and emotional support
- Empowering Canadians to take charge of their blood cancer experience through practical support and advocacy

Advocacy for Canadian Childhood Oncology Research Network (Ac2orn) - http://www.ac2orn.com
Ac2orn is committed to advocating for translational research and effective treatments to realize the goal of curing childhood, adolescent, and young adult cancers. Ac2orn is a national organization made up of childhood, adolescent, and young adult cancer advocates and survivors, across all cancer types, and in different stages of the cancer experience.

Ontario Parents Advocating for Children with Cancer (OPACC) - http://www.opacc.org/
OPACC will be the leading voice and expert resource for families and organizations navigating the childhood cancer journey.

Childhood Cancer Canada - https://www.childhoodcancer.ca/
Childhood Cancer Canada's mission is to create victories for Canadian children with cancer through investment in national, collaborative, lifesaving research, empowering education, and community programs.

2. Information Gathering

One online survey was created through SurveyMonkey. Information was gathered in July and August 2024. The survey was distributed in both French and English through various social media channels and directly by email.

The survey asked for input from patients and caregivers who have lived experience with blinatumomab (Blincyto) for the treatment of pediatric ALL.

9 respondents participated in this survey. 8 respondents (88.89%) indicated that they were the caregiver of an ALL patient (past or present). 1 respondent indicated that they were a caregiver of an ALL patient (past or present).

Respondents were asked to identify the age range of the person diagnosed with ALL at the time of diagnosis. 8 respondents answered this question.

4 (50%) answered 5-14 years old

2 (25%) answered 1-4 years old

1 (12.5%) answered 15-18 years old

1 (12.5%) answered 19-29 years old

Respondents who answered 19 years + were disqualified from the survey. Respondents who did not answer this question were also disqualified from the survey.

7 respondents identified their primary residence:

Ontario - 6/7 (85.71%)

British Columbia – 1/7 (14.29%)

As this treatment has previously been reviewed in pediatric ALL, input from this population of patients and/or caregivers regarding disease experience and experience with currently available treatments has previously been gathered and submitted to the CDA (formerly CADTH) for consideration.

So as not to cause emotional exhaustion and undue harm to this affected population, these most recent surveys focused on questions regarding experience with the treatment under review, blinatumomab (Blincyto) in pediatric ALL, and the possibility of improving access to include earlier lines of treatment for pediatric ALL patients.

Some previously gathered and submitted input from this patient population has been used in this patient group input submission as well. Previous review found here - https://www.cadth.ca/blinatumomab-blincyto-acute-lymphoblastic-leukemia-pediatric-details

3. Disease Experience

Pediatric patients with Philadelphia chromosome-negative (Ph-) relapsed/refractory B precursor acute lymphoblastic leukemia (ALL) in their first relapse face a difficult journey with their disease, and the impacts of relapse are profound and multifaceted.

Physically, these children may experience a variety of symptoms, including severe fatigue, pain, high fevers, bleeding, bruising, bone pain, and swollen lymph nodes, but the impacts of pediatric cancer relapse on the child and their family extend past physical symptoms.

Relapse and the risks associated with immunosuppression can significantly limit interactions with others and interfere with normal activities like attending school, playing with friends, and participating in extracurricular activities. The physical and emotional toll of the disease and its treatments can diminish the child's ability to enjoy life and engage in activities they once loved. This impact extends to other family members as well including parents and siblings as the heightened risk of infection creates a considerable burden for everyone involved.

Families often experience intense emotional stress due to their child's condition and the uncertainty of the outcome. A relapse can escalate stress, anxiety, and fear about the future. Caregivers do not have time to care for themselves and often their mental health is severely impacted. Prolonged illness and ongoing treatment may contribute to feelings of sadness or depression, helplessness and emotional exhaustion. Parents may also need to take time off work to care for their child and may have additional expenses due to their child's illness, resulting in financial strain.

Broadly, a pediatric cancer relapse affects every aspect of a family's life, from the child's health and emotional state to the family's financial stability and daily dynamics. Support systems and coping strategies are crucial for managing these challenges and maintaining resilience during such a difficult time.

Survey respondents were asked to identify the specific diagnosis of the ALL patient. Responses are reflected in the chart below.

ANSWER CHOICES		RESPONSES	
Philadelphia Chromosome-Positive ALL		0.00%	0
Philadelphia Chromosome-Negative ALL		0.00%	0
B-Cell ALL		75.00%	6
T-Cell ALL		0.00%	0
Acute B-lymphocytic leukemia		12.50%	1
Acute precursor B Cell leukemia		0.00%	0
Pre-B cell lymphocytic leukemia		0.00%	0
Acute T-lymphocytic leukemia		12.50%	1
Other (please specify)	Responses	0.00%	0
TOTAL			8

4. Experiences With Currently Available Treatments

The standard of care for treating relapsed or refractory pediatric ALL typically involves a combination of strategies, including drug therapy and radiation. For patients with refractory disease, these aggressive treatments often result in serious side effects, such as immunosuppression, severe pain, infections, anemia, and organ damage, which can significantly impact the child's quality of life.

There stands a significant unmet need for more effective and tolerable therapies for patients who relapse after first-line treatment, particularly those that provide a better quality of life than traditional chemotherapy by reducing symptom burden and offering a lower toxicity profile.

Additionally, there is an ongoing need for outpatient therapeutic options that minimize the need for frequent hospital visits and extended stays. These visits can disrupt daily routines and normal activities, such as school, play, and family time. Hospital environments also pose risks of infections and other complications, especially for patients with weakened immune systems due to cancer or treatment. The physical demands of traveling to and staying in the hospital, combined with the effects of treatment, can contribute to physical fatigue and discomfort. Prolonged hospital visits can lead to heightened stress and anxiety for children who may feel isolated from their usual environment and activities. This can create fear and uncertainty about their health and future, diminishing their quality of life and impacting their overall well-being and happiness. Prolonged hospital stays can be emotionally draining for children, affecting their mood, behavior, and outlook on treatment.

For families, frequent hospital visits can disrupt family routines, including work schedules and siblings' activities. Additional support, such as transportation and meal assistance, is often needed, adding to the overall burden. Providing more outpatient treatment options could significantly ease these challenges and improve quality of life for patients and their families.

5. Improved Outcomes

For better outcomes in treatment, patients and their families are looking for options that are not only effective but also gentle on their children. They seek innovative therapies that can provide significant benefits without causing undue harm or severe side effects. Additionally, having these treatments covered by drug plans is crucial, as it alleviates the financial burden and ensures that their child receives the necessary care without additional stress. Overall, parents want a comprehensive approach that combines efficacy with compassion, innovation, and financial accessibility to support their child’s journey through treatment.

Respondents were asked, If blinatumomab (Blincyto) treatment could be given to patients in their first relapse, and this could potentially lower the risk of a second relapse. Would this influence your decision on whether to undergo the treatment again? 5 respondents answered this question.

5/5 (100%) answered – “Would definitely influence my decision”

Respondents shared their thoughts:

“We weren’t given Blina for relapse, but for treatment resistant B-ALL. But in a situation if there was a relapse and Blina was an option, we would absolutely go forward with Blina. It was a good experience.”

“BLINA Should be used in every diagnosis of ALL. It was effective and it was gentle. I understand it is expensive and honestly, I don’t care how much it costs. It should be covered by insurance, and it should be added to the old, outdated chemo protocol.”

6. Experience With Drug Under Review

Survey respondents reported positive experiences with blinatumomab treatment, emphasizing its benefits for both patients and caregivers. Participants noted that the administration of blinatumomab was generally straightforward, contributing to a smooth treatment process. They also highlighted the observed low symptom burden, which significantly reduced the impact of the treatment on the patients' daily lives and overall well-being. This ease of administration and minimal side effects were praised as key advantages of blinatumomab in managing pediatric ALL

Respondents were asked, Has the ALL patient taken blinatumomab (Blincyto) as a treatment for ALL?

7/7 respondents (100%) answered - YES

Respondents were asked, How difficult was the process of receiving blinatumomab (Blincyto) infusions for the patient? 5 respondents answered this question.

3/5 (60%) answered “Easy”
1/5 (20%) answered “Neutral”
1/5 (20%) answered “Very Easy”
0 respondents answered “Difficult” or “Very Difficult”

Some respondents elaborated on the ease of this treatment for the patient:

- “My daughter felt great while on the blina. Our monitor did beep a lot the first two infusions and we would have to drive two hours to London Ontario to have the nurses reset the machine. The third bag of BLINA seemed to work the best, but it seemed like the storage bag was different, which we found a big difference in to keep the line from filling up with champagne bubbles”
- “Needle changes every week are upsetting but otherwise pretty easy”
- “Only difficult part was going to the hospital every 4 days to change the bag. But my son felt great on this treatment”
- “The pharmacy that we dealt with (LHSC, Victoria Campus) and the oncology staff made it very simple and easy for us to obtain this medication”

Respondents were asked, How difficult was the process of receiving blinatumomab (Blincyto) infusions for the caregiver(s)? 5 respondents answered this question.

2/5 (40%) answered “Neutral”
2/5 (40%) answered “Easy”
1/5 (20%) answered “Very Easy”
0 respondents answered “Difficult” or “Very Difficult”

Some respondents elaborated on the ease of this treatment for the caregiver(s):

- “She felt well, so that made me feel good. She would be up and dancing and no normal chemo side effects My only concern was the beeping from the IV monitor, the bubbles that would be produced in the bag, and her line being caught on something”
- “Travel to the hospital every 4 days is a bit of a pain, but otherwise it’s pretty easy”

Respondents agreed that, even if they had experienced challenges in administering blinatumomab, they would still choose this treatment due to its success in achieving remission and its minimal side effects.

Respondents were asked, If you experienced difficulty with the administration of blinatumomab infusions, would you still consider undergoing the treatment again if needed? 3 respondents answered this question.

3/3 (100%) answered “Would definitely consider”

Respondents elaborated:

- “This medication was what put our daughter into remission prior to her undergoing a bone marrow transplant for treatment resistant B-ALL. The nature of the medication allowed for a two month (she had two cycles of Blina) vacation from the hardship effects of chemotherapy. She got some energy back and was able to build up, physically and mentally prior to her BMT, which was vital to her so far very successful outcome. Blina was key in this, both in its’ relatively small amount of side effects and its success in putting her into remission.”
- “BLINA Seemed to be much much easier on her than the harsh side effects of traditional chemotherapy.”

Respondents collectively emphasized the desire for a smooth, efficient, and less hospital-dependent treatment experience.

Respondents were asked, How could the process of administering blinatumomab infusions in hospital have been made more manageable by the system for patients and/or caregiver(s)? This was an open-ended question. 5 respondents answered this question.

- “If the nurses had more practice/experience with bag changes”
- “Faster processing times”
- “We had to stay in hospital for a few days as a monitor while the liner ran, I believe for 48 hours. It was a hospital admission, but it was OK”
- “We take the bag with us so there are no hospital infusions”
- “It was very straightforward and manageable. No suggestions for how to make it more manageable.”

Respondents were able to adapt and use practical strategies to fit their child's needs to make administration of blinatumomab more manageable.

Respondents were asked, Were there strategies that you personally used to make the administration more manageable for the patient and/or the caregiver(s)? This was an open-ended question. 3 respondents answered this question.

- “Used our own backpack (a kids hydration backpack)”
- “Our 11 year old daughter was very aware and responsible for the backpack and attached line. She was careful enough with it all and there were very little/no mechanical complications to the medication being infused”
- “We found an amazing bag that held it up and it was small for her to wear. I would recommend this bag to any child with blina”

7. Companion Diagnostic Test

8. Anything Else?

blinatumomab addresses an important unmet need by offering a more effective and tolerable treatment option compared to traditional chemotherapy and can be particularly beneficial for those experiencing their first relapse. blinatumomab has been shown to improve overall survival and achieve remission in patients who have not responded well to other treatments. This treatment option may offer fewer long-term side effects, such as organ damage and neurocognitive issues, which are crucial considerations for this still-growing pediatric population. The therapy's reduced toxicity contributes to a significant improvement in quality of life. Patients often experience less severe side effects, reducing the physical and emotional strain of treatment.

One of the remarkable advantages of blinatumomab is its administration, which can be managed on an outpatient basis. This contrasts with some traditional treatments that require extended hospital stays. By reducing the need for prolonged hospitalization, blinatumomab minimizes disruptions to daily life, such as schooling and social activities, which is particularly beneficial for children and their families, making it a more manageable option. Fewer hospitalizations offers a more stable daily routine, allowing children to remain in a familiar and supportive home environment during treatment which can be crucial for maintaining overall well-being and can positively affect long-term outcomes.

blinatumomab's potential to achieve remission and reduce the need for more intensive therapies or extended hospitalizations could offer cost-effectiveness. By potentially lowering the overall treatment burden and associated healthcare costs, it represents a valuable option for improving outcomes in this challenging patient population.

Overall, blinatumomab represents a promising alternative to traditional chemotherapy, offering a balance of efficacy and reduced toxicity. It aligns with patients' values and the need for innovative and effective therapies that enhance the quality of life for pediatric patients.

Collectively, our patient organizations would strongly recommend that the CDA endorse the reimbursement of blinatumomab (Blincyto) for the treatment of pediatric patients with Philadelphia chromosome negative relapsed/refractory B precursor acute lymphoblastic leukemia (ALL) who are in first relapse.

We would also like to note that as advocates for those affected by pediatric ALL, our organizations collectively want to emphasize a key concern regarding the well-being of this patient population. Numerous reviews in recent years have explored the use of blinatumomab for treating pediatric ALL in various lines of treatment and our patient organizations are concerned that continuously asking these patients and/or their caregivers to recount their experiences with this treatment may lead to emotional exhaustion. We are apprehensive that continuously revisiting these issues could place an undue burden on these individuals.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Amgen Inc.				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Colleen McMillan
Position: Advocacy Lead
Patient Group: The Leukemia & Lymphoma Society of Canada (LLSC)
Date: August 12, 2024

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: **PX0367-000**

Generic Drug Name (Brand Name): **blinatumomab (Blincyto)**

Indication: Indicated for the pediatric patients with Philadelphia chromosome negative relapsed/refractory B precursor acute lymphoblastic leukemia (ALL) who are in first relapse.

Name of Clinician Group: Pediatric Oncology Group of Ontario

Author of Submission: Dr. Paul Gibson

1. About Your Clinician Group

POGO is a collaboration of Ontario's 5 specialized childhood cancer centres and the official advisor to the Ministry of Health and Long-Term Care on pediatric cancer care and control. This submission represents a collaboration of pediatric cancer clinicians from across the province with membership informed by POGO's Therapeutic and Technology Advisory Committee (TAC). For more information on POGO, please visit www.pogo.ca

2. Information Gathering

This submission was prepared in a consultative manner. Dr. Gibson discussed the indication with members of the submission panel and sought input from the POGO TAC. Dr. Gibson subsequently drafted the initial response and all others contributing to the submission reviewed and edited the draft that has led to this final submission.

3. Current Treatments and Treatment Goals

Pediatric Acute Lymphoblastic Leukemia (ALL) is the most common pediatric malignancy. Approximately 80% of all new cases of ALL are of B lineage (B-ALL). Upfront B-ALL is treated primarily by risk stratified, multi-agent chemotherapy. A small proportion of newly diagnosed patients may also receive cranial radiation, allogeneic stem cell transplant and/or cellular therapies. While upfront relapse free survival continues to gradually improve, relapsed B-ALL remains a common challenge in pediatric oncology.

Much like in upfront therapy, the approach to treating relapsed B-ALL is stratified by risk with particular attention placed towards the timing of the relapse and the site of the relapse (bone marrow versus extramedullary). The current approach of the Children's Oncology Group and most Canadian Pediatric Oncology centres is as follows (Brown, JAMA, 2021):

Risk Group	Criteria
High Risk	• bone marrow (includes isolated bone marrow and combined bone marrow and extramedullary) relapse less than 36 months after diagnosis • OR • isolated extramedullary relapse less than 18 months after diagnosis
Intermediate Risk	• Bone marrow relapse at least 36 months after diagnosis OR isolated extramedullary relapse at least 18 months after diagnosis • AND • MRD post 1 cycle of reinduction greater than or equal to 0.1%
Low Risk	• Bone marrow relapse at least 36 months after diagnosis • OR • Isolated extramedullary relapse at least 18 months after diagnosis and MRD less than 0.1%.

The Children's Oncology Group Study AALL 1331 defined a new standard of care for all pediatric patients with relapsed B-ALL, across all risk groups. Unfortunately, until this point, reimbursement has not kept pace with this standard.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

While more and more evidence accumulates for blinatumomab in the upfront setting, there is remains a clear need for it in the relapsed setting. Prior to the AALL 1331 results being known, intermediate and high-risk patients were mostly commonly treated with 3 cycles of intensive cytotoxic chemotherapy requiring extensive hospitalization and supportive care prior to proceeding to allogeneic stem cell transplant. In AALL 1331, the HR and IR randomization was terminated early due to clinically significant impact and showed superior disease-free survival in the blinatumomab arm (54.4% vs 39% with hazard ratio for disease progression or mortality, 0.70 [95% CI, 0.47-1.03]); 1-sided *P* = .03). There was marked decrease in toxicity in the blinatumomab arm including infection (15% vs 65%), sepsis (2% vs 27%) and mucositis (1% vs 28%). These dramatic toxicity differences almost certainly results in increased tolerability of the blinatumomab arm with less hospital inpatient resource utilization and improved patient quality of life.

We note that as presently written, the goal of this review is to compare Arms C and D of AALL 1331 despite the compelling evidence noted in ARMS A and B. Of note, Intermediate risk patients would be eligible for reimburse as per a past CADTH/CDA review (pCODR 10204) due to their MRD positivity. High Risk patients who happen to be MRD negative post the first reinduction are therefore NOT eligible currently for reimbursement. We strongly suggest the scope of this review include these patients also.

Prior to the AALL 1331 results being known, low risk patients treated off study received the same 3 intensive blocks of chemotherapy that high and intermediate risk patients did before moving on to continuation/consolidation blocks and maintenance. These patients avoid the toxicity and late effects of allogeneic transplant. AALL 1331 added 3 courses of blinatumomab to standard therapy and excluded the 'Block Three' cytotoxic chemotherapy arm. Block 3 includes both High Dose cytarabine and Intermediate Dose methotrexate. Both therapies require extensive hospitalization and carry a significant risk of infection, sepsis and severe mucositis. The blinatumomab arm showed clear impact in patients in relapse with bone marrow involvement not only improving their outcomes, but also avoiding the toxicity of Block C.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

AALL 1331 created a new standard of care in pediatric B-ALL in first relapse with bone marrow involvement. It provides not only superior disease control, but also decreases toxicity. This is true for low, intermediate and high-risk patients.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

All patients with B-ALL in first relapse should receive blinatumomab, with important exception or patients presenting with low-risk isolated extramedullary disease, primarily, those with isolated CNS relapse. Blinatumomab is known to have poor CNS penetration and therefore is not surprising to note that this group was not aided by the addition of blinatumomab. This group is likely better served at present by utilizing older protocols that focus on intensive high dose cytarabine and methotrexate cycles.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Cytokine Release Syndrome (CRS) and CNS toxicity are the most important adverse events noted while administering blinatumomab. Treating centres should be aware of these toxicities and monitor appropriately. In rare cases, tocilizumab may be required to address CRS not responsive to holding the infusion and corticosteroid treatment. In most cases, initiation of therapy as inpatient is appropriate.

Treatment response is monitored regularly by assessment of peripheral blood counts and bone marrow. For patients undergoing MRD assessment by flow cytometry after blinatumomab, a non-CD19 dependent methodology should be employed.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

There are two primary factors that would lead to discontinuation are lack of response and recurrent unmanageable toxicity. Disease persistence, be it noted by circulating lymphoblasts or persistent MRD should lead to consideration of discontinuation in favour of other therapy. CRS and/or CNS toxicity that persists despite the use of lower doses and/or corticosteroids also warrants a switch in therapy.

5.5 What settings are appropriate for treatment with blinatumomab? Is a specialist required to diagnose, treat, and monitor patients who might receive blinatumomab?

Blinatumomab therapy should be initiated under the care of a centre specialized in pediatric oncology. Following its initiation however, patients who tolerate the infusion can have the 'bag changes' required for continuous infusion handled in community hospitals and clinics, provided the training and reimbursement can be facilitated.

6. Additional Information

Future reimbursement strategies of blinatumomab must include consideration of drug wastage. There are 3 primary mechanisms of wastage. The first is the extra drug needed to prime and fill the line from the pump to the patient. In Ontario, this is currently accounted for in reimbursement. Secondly, there is wastage of vial contents left over after preparing an infusion. This is very common in pediatrics, where patients are unlikely to require 'full adult dose' preparations. This is currently not reimbursed. Finally, there is drug lost due to unplanned infusion interruptions (infusion pauses for toxicity management, CADD pump failure, infusion like cracking, etc.). This is a practical concern in giving this medication and reimbursement strategies should acknowledge it. Fulsome reimbursement that includes wastage is crucial to ensure equitable access to this therapy across jurisdictions.

Evidence of blinatumomab's utility in upfront B-ALL therapy is growing, both in adults and pediatrics. While the use in first relapse remains a critical need in pediatric cancer, data will soon be shared with CDA suggesting an even larger demand in the upfront setting. Nevertheless, we think it crucial that there be reimbursement for relapsed patients as this reflects the current standard of care.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

   None

Declaration for Clinician 1

Name: Dr. Paul Gibson
Position: Pediatric Oncologist, McMaster Children's Hospital, POGO Associate Medical Director
Date: 08-08-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Ms. Sue Zupanec
Position: Nurse Practitioner, Section of Leukemia and Lymphoma, The Hospital for Sick Children
Date: 09-08-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Vicky Breakey
Position: Pediatric Hematologist/Oncologist, Division Chief, McMaster Children's Hospital
Date: 09-08-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Ms. Paula MacDonald
Position: Clinical Pharmacist, McMaster Children's Hospital
Date: 09-08-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Laura Wheaton
Position: Pediatric Oncologist, Kingston Health Sciences Centre
Date: 08-09-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Salah Ali
Position: Pediatric Oncologist, Kingston Health Sciences Centre
Date: 08-08-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Dr. Sumit Gupta
Position: Pediatric Oncologist, Section Head, Leukemia and Lymphoma, The Hospital for Sick Children
Date: 09-08-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Dr. Jennifer Seelisch
Position: Pediatric Oncologist, Children's Hospital, London Health Sciences Centre
Date: 08-08-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Dr. Donna Johnston
Position: Pediatric Oncologist, Children's Hospital of Eastern Ontario
Date: 10-08-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Jazz Pharmaceuticals	X			
Alexion Pharmaceuticals	X			
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Tejinder (TJ) Bains
Position: Pediatric Oncology Pharmacist, Children's Hospital of Eastern Ontario
Date: 12-08-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Jazz Pharmaceuticals	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: Dr. Alexandra Zorzi
Position: Division Head, Pediatric Hematology/Oncology, Children's Hospital, London Health Sciences Centre
Date: 08-08-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 12

Name: Stephanie Cox
Position: Pediatric Oncology Nurse Practitioner, McMaster Children's Hospital
Date: 12-08-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

CDA-AMC Non-Sponsored Reimbursement Review

Industry Input

CADTH Project Number:	PX-0367
Generic Drug Name:	blinatumomab
Indication:	Indicated for pediatric patients with Philadelphia chromosome negative relapsed/refractory B precursor acute lymphoblastic leukemia (ALL) who are in first relapse
Name of Organization:	Amgen Canada Inc.
Author of Submission:	[redacted]

1. Does the proposed project scope accurately reflect the treatment landscape?

The proposed project to evaluate whether blinatumomab should be publicly reimbursed in pediatric patients with Philadelphia chromosome negative relapsed/refractory B precursor acute lymphoblastic leukemia (B-ALL) who are in first relapse is reflective of the current treatment landscape as described in NCCN[1] and ESMO[2] treatment guidelines. While blinatumomab has been broadly approved by Health Canada for use in relapsed pediatric patients[3], it is not currently publicly reimbursed for pediatric patients in first relapse.

As described in the criteria of the project scope, only low risk (LR) pediatric patients in first relapse are being considered (i.e. arm D of AALL1331) despite the AALL1331 trial also including high- and intermediate-risk (HR/IR) pediatric patients in first relapse (i.e. arm B of ALL1331).[4] Patients defined as high-risk relapse have a poorer prognosis compared with the other risk groups and as such a higher unmet need.[5] Given the results of the AALL1331 trial[5,6] as well as Study 20120215[7], the proposed project should also include high- and intermediate-risk (HR/IR) pediatric patients in first relapse within the scope of this review.

2. Are you aware of relevant published studies that you would like considered in the clinical review?

Study AALL1331, conducted by the Children's Oncology Group (COG) and sponsored by the National Cancer Institute, was a phase 3, open-label, randomized, parallel group study to evaluate efficacy and safety of blinatumomab compared with standard combination chemotherapy in treating pediatric patients with B-ALL in first relapse.[5] This was a group wide risk-stratified study to test whether

incorporation of blinatumomab into the treatment of patients with childhood B-ALL at first relapse will improve disease-free survival (DFS, primary endpoint). In September 2019, Study AALL1331 was closed to accrual for the high-risk and intermediate-risk arms while the low-risk group continue to enroll and randomize patients until enrollment goals were reached. Closure of the HR/IR arm was based on the recommendation of the COG Data Monitoring Committee (DMC), due to a strong trend towards improved DFS and improved Overall Survival (OS), markedly lower rates of serious toxicity, and a higher rate of minimal residual disease (MRD) clearance for blinatumomab compared to chemotherapy. Results from the HR/IR were first presented at ASH 2019 as a late-breaking abstract and subsequently published by Brown et al. in 2021 the The Journal of the American Medical Association.[5]

In addition to the analysis from Arms C and D from the AALL1331 trial in the proposed project scope,[6] we recommend that the following publications be considered in the clinical review. These studies support the efficacy, safety and tolerability of blinatumomab in patients with high- and intermediate-risk (HR/IR) first relapse B- ALL.

1) **Effect of Postreinduction Therapy Consolidation With Blinatumomab vs Chemotherapy on Disease-Free Survival in Children, Adolescents, and Young Adults With First Relapse of B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. (Study AALL1331, NCT02101853).[5]**

   The objective of this analysis was to determine whether substituting blinatumomab for intensive chemotherapy in consolidation therapy would improve survival in children, adolescents, and young adults with HR/IR first relapse of B-ALL. After reinduction chemotherapy, subjects in the HR/IR group were randomized to receive consolidation treatment with 2 cycles of chemotherapy or 2 cycles of blinatumomab. On completion of randomized therapy, eligible subjects underwent hematopoietic stem cell transplantation (HSCT). The primary end point was DFS and the secondary end point was OS. At the time when randomization was terminated, 80 of 131 planned events had occurred. With 2.9 years of follow-up, 2-year DFS was 54.4% for the blinatumomab arm vs 39.0% for the chemotherapy arm (Hazard Ratio [HR], 0.70 [95% CI, 0.47-1.03]; 1-sided P=.03) and OS was 71.3% vs 58.4% (HR, 0.62 [95% CI, 0.39-0.98]; 1-sided P=.02). Safety results for blinatumomab in this population of subjects were generally consistent with the results reported in previous studies of blinatumomab. No new safety signals were identified in Study AALL1331.

2) **Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children With High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia (Study 20120215, NCT02392859).[7]**

Study 20120215 was a randomized, open-label, controlled, phase 3 study to investigate the efficacy, safety, and tolerability of blinatumomab as part of consolidation therapy versus conventional consolidation chemotherapy in pediatric subjects with high-risk first relapse B-cell precursor ALL. Following induction and 2 blocks of high-risk consolidation chemotherapy, subjects with M1 (< 5% blasts) or M2 (≥ 5% and < 25% blasts) bone marrow could enter Study 20120215 and be randomized to 1 consolidation cycle of blinatumomab or a third block of consolidation chemotherapy (HC3). The primary endpoint of this study was event-free survival (EFS). The key secondary endpoint was OS and other secondary endpoints included MRD response and adverse event incidence. EFS was significantly improved in the blinatumomab arm compared with the HC3 arm. The incidence of events in the blinatumomab arm vs HC3 arm was 31% vs 57% (p<.001; HR, 0.33 [95%CI: 0.18, 0.61]). The OS hazard ratio was 0.43 (95% CI: 0.18 to 1.01). MRD remission was observed in 90% (44/49) patients in the blinatumomab vs 54% (26/48) in the HC3 arm; difference, 35.6% [95% CI, 15.6%-52.5%]. Safety results for blinatumomab in this population of subjects were generally consistent with the results reported in previous studies of blinatumomab. No new safety signals were identified in Study 20120215.

1) Do you have additional comments that you feel are pertinent to this review?

Inclusion of the high- and intermediate-risk categories within the scope of reviewing blinatumomab for reimbursement in pediatric patients with Ph- B-cell precursor ALL who are in first relapse is supported by the regulatory review of blinatumomab in this indication. On 29 August 2023, Health Canada converted the conditional approval to full approval for the indications below:

- Patients with Philadelphia chromosome-negative CD19 positive B-cell precursor acute lymphoblastic leukemia (ALL) in first or second hematologic complete remission with minimal residual disease (MRD) greater than or equal to 0.1%
- Pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL

Study 20120215 was submitted as the confirmatory study for both indications.

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2. Hoelzer D, Bassan R, Boissel N, et al. Clinical Practice Guideline interim update on the use of targeted therapy in acute lymphoblastic leukaemia. *Annals of Oncology*. 2023;35(1):15-28. Published 2023 Oct 11. doi: 10.1016/j.annonc.2023.09.3112

3. Amgen Canada Inc. Product Monograph: BLINCYTO (blinatumomab for injection). Published online 2024.

4. Winters A, Gore L. Moving immunotherapy into the front line in ALL. *Hematology. American Society of Hematology*. Education Program. 2019 Dec;2019(1):209-217. doi: 10.1182/hematology.2019000017.

5. Brown PA, Ji L, Xu X, et al. Effect of Postreinduction Therapy Consolidation With Blinatumomab vs Chemotherapy on Disease-Free Survival in Children, Adolescents, and Young Adults With First Relapse of B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. *JAMA*. 2021;325(9):833–842. doi:10.1001/jama.2021.0669.

6. Hogan LE, Brown PA, Ji L, et al. Children's Oncology Group AALL1331: Phase III Trial of Blinatumomab in Children, Adolescents, and Young Adults With Low-Risk B-Cell ALL in First Relapse. J Clin Oncol. 2023 Sep 1;41(25):4118-4129. Published 2023 May 31. doi: 10.1200/JCO.22.02200.

7. Locatelli F, Zugmaier G, Rizzari C, et al. Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children With High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. *JAMA*. 2021;325(9):843-854. doi:10.1001/jama.2021.0987.