DRAFT Reimbursement Review

Working Papers

BLINATUMOMAB (BLINCYTO)

(Non-Sponsored Review)

Therapeutic area: Acute lymphoblastic leukemia, pediatrics

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Table of Contents

List of Tables 4
List of Figures 4
Abbreviations 5
Background Appendices 6
Appendix 1: Drug Program Input and Treatment Characteristics 6
Clinical Review Appendices 6
Appendix 2: Methods of the Systematic Review 6
Appendix 3: Methods of the Studies Included in the Systematic Review 14
Appendix 5: Place in Therapy 21
Economic Review Appendices 22
Appendix 6: Cost Comparison Table 22
References 38

List of Tables

Table 1. Systematic Review Eligibility Criteria 6
Table 2: Syntax Guide 7
Table 3. Excluded Studies 14
Table 4: Risk Definitions Used in the Included Studies 14
Table 5: Consolidation chemotherapy regimen used in Locatelli et al. (2021) 17
Table 6: Reinduction Treatment according to UKALL R3 Protocol[a] and used in COG AALL11331 17
Table 7: Consolidation Chemotherapy Schedule in the COGAALL1331 Intermediate- and High-Risk Group 18
Table 8: Postreinduction Chemotherapy Schedule in the COGAALL1331 Low-Risk Group 19
Table 9: COGALL1331 Low-Risk Subgroup Analysis by Disease Site 20
Table 10: CDA-AMC Cost Comparison Table for Pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor (ALL) – low-risk patients 23
Table 11: CDA-AMC Cost Comparison Table for Pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor (ALL) – intermediate and high-risk patients 31

List of Figures

Figure 1: COGAALL1331 Study Design 16

Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
B-ALL	B-cell precursor acute lymphoblastic leukemia
BFM	Berlin-Frankfurt-Münster
BM	bone marrow
CI	confidence interval
CNS	central nervous system
COG	Children's Oncology Group
CR	complete remission
CRS	cytokine release syndrome
DFS	disease-free survival
EFS	event-free survival
EM	extramedullary
HR	hazard ratio
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplant
ICANS	immune effector cell-associated neurotoxicity syndrome
IR/HR	intermediate- and high-risk
IEM	isolated extramedullary relapse
IntReALL	International study for treatment of childhood relapsed acute lymphoblastic leukemia
ITT	intention to treat
IV	intravenous
LR	low risk
MRD	minimal residual disease
OR	odds ratio
OS	overall survival
NR	not reported
Ph	Philadelphia
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
T-ALL	T-cell precursor acute lymphoblastic leukemia
WDAE	withdrawal due to adverse event

Background Appendices

Appendix 1: Drug Program Input and Treatment Characteristics

The drug programs provide input on each drug being reviewed through the Reimbursement Review process by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review are summarized and provided to the expert committee in a separate document.

Clinical Review Appendices

Appendix 2: Methods of the Systematic Review

Systematic Review Eligibility Criteria

Table 1. Systematic Review Eligibility Criteria

Criteria	Description
Population	Patients aged 1 to 18 years old with Philadelphia chromosome negative B-cell precursor ALL (B-ALL) who are in first relapse~~, with or without extramedullary disease~~. Subgroups: (risk of resistance/relapse post-induction); definitions from Children's Oncology Group trials • Low-risk – bone marrow (BM) relapse with or without extramedullary (EM) disease (BM±EM) ≥36 months or isolated EM (IEM) relapse ≥18 months from initial diagnosis, low (<0.1%) MRD or MRD unknown at the end of reinduction chemotherapy • Intermediate-risk – same as low risk but MRD ≥ 0.1% • High-risk – isolated BM (iBM) and combined BM/EM relapse <36 months after diagnosis or IEM relapse <18 months after diagnosis
Intervention	Blinatumomab 15 mcg/m^2 once daily as continuous intravenous infusion over 28 days
Comparator	Multi-drug Chemotherapy
Outcomes	**Efficacy outcomes:** OS, EFS, DFS, CR, MRD, time to next relapse, ability to proceed to HSCT, HRQoL **Harms outcomes:** Any grade AEs, SAEs, Grade ≥3 AEs, WDAEs, mortality, AESIs (CRS, neurologic events [encephalopathy, seizures, febrile neutropenia, ICANS], infections)
Study design	published and unpublished Phase III and IV RCTs

AE = adverse event; AESI = adverse event of special interest; CR = complete remission; CRS = cytokine release syndrome; DFS = disease-free survival; EFS = event-free survival; HRQoL = health-related quality of life; HSCT = hematopoietic stem cell transplantation; ICANS = immune effector cell-associated neurotoxicity syndrome; IV = intravenous, MRD = minimal residual disease; OS = overall survival; SAE = serious adverse event; WDAE = withdrawal due to adverse event

Search Strategy

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[1]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's

MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were blinatumomab, B-ALL, and pediatrics. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

Search filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results.

The initial search was completed on July 10, 2024. Regular alerts updated the search until the meeting of the Formulary Management Expert Committee (FMEC) on November 21, 2024.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency). Google was used to search for additional internet-based materials.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts.

A focused literature search for indirect treatment comparisons (ITCs) dealing with blinatumomab or B-ALL was run in MEDLINE on July 10, 2024. Retrieval was not limited by publication date or by language.

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.
Date of search: July 10, 2024
Alerts: Biweekly search updates until project completion
Search filters applied: Randomized controlled trials and controlled clinical trials
Limits

- Publication date limit: none
- Language limit: none
- Conference abstracts: excluded

Table 2: Syntax Guide

Syntax	Description

/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*****	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.jw	Journal title word (MEDLINE)
.jx	Journal title word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Warning

To conduct a comprehensive search, we may have included antiquated, noninclusive, or potentially stigmatizing terms that may have appeared in past and present literature. We recognize and acknowledge the inappropriate and harmful nature of terms that may appear in search strategies and include this warning so the reader can determine how they would like to proceed.

The warning is modified from the University of Michigan Library's guidance, Addressing antiquated, non-standard, exclusionary, and potentially offensive terms in evidence syntheses and systematic searches.

Multi-Database Strategy

1 (Blincyto* or blinatumomab* or MT-103 or MT103 or AMG-103 or AMG103 or MEDI-538 or MEDI538 or 4FR53SIF3A).ti,ab,ot,kf,hw,nm,rn.

2 exp Precursor B-Cell Lymphoblastic Leukemia-Lymphoma/

3 ((B-Cell or B-Cells or BCP or B acute or B precursor or precursor B or pre B or B lymphoblastic) and (leuk?emia* or lymphoma* or ALL)).ti,ab,kf.

4 (B lymphocyt* and (leuk?emia* or lymphoma* or ALL)).ti,ab,kf.

5 B-ALL.ti,ab,kf.

6 or/2-5

7 Pediatrics/ or Hospitals, Pediatric/ or Intensive Care Units, Pediatric/ or Adolescent/ or exp Child/ or exp Infant/ or Pediatric Nursing/ or Child, Hospitalized/ or Adolescent, Hospitalized/

8 (child* or infant* or baby or babies or newborn* or newborns or neonate or neonates or neonatal or preemie? or infancy or paediatric* or pediatric* or toddler* or girl? or boy? or kid? or teen or teens or teenage* or youngster? or youth* or preteen* or adolescent* or adolescence or preschooler* or pre-schooler* or nursery school* or daycare* or school age? or (months adj2 age) or (month? adj2 old) or preadolescen* or juvenile* or prepubescen* or prepubert* or pre-pubescen* or pre-pubert* or pre-adolescen*).ti,ab,kf.

9 (pediat* or paediat* or child* or adolescen* or juvenile*).jw.

10 or/7-9

11 and/1,6,10

12 11 use medall

13 *blinatumomab/ or (Blincyto* or blinatumomab* or MT-103 or MT103 or AMG-103 or AMG103 or MEDI-538 or MEDI538).ti,ab,kf,dq.

14 exp Acute Lymphoblastic Leukemia/ and (B-Cell or B-Cells or BCP or B acute or B precursor or precursor B or pre B or B lymphoblastic or B lymphocyt*).ti,ab,kf,dq.

15 ((B-Cell or B-Cells or BCP or B acute or B precursor or precursor B or pre B or B lymphoblastic) and (lymphocyt* or lymphoblastic or lymphoid or lymphatic) and (leuk?emia* or lymphoma* or ALL)).ti,ab,kf,dq.

16 (B lymphocyt* and (leuk?emia* or lymphoma* or ALL)).ti,ab,kf,dq.

17 B-ALL.ti,ab,kf,dq.

18 or/14-17

19 exp pediatrics/ or pediatric hospital/ or pediatric intensive care unit/ or exp adolescent/ or exp child/ or exp pediatric nursing/

20 (child* or infant* or baby or babies or newborn* or newborns or neonate or neonates or neonatal or preemie? or infancy or paediatric* or pediatric* or toddler* or girl? or boy? or kid? or teen or teens or teenage* or youngster? or youth* or preteen* or adolescent* or adolescence or preschooler* or pre-schooler* or nursery school* or daycare* or school age? or (months adj2 age) or (month? adj2 old) or preadolescen* or juvenile* or prepubescen* or prepubert* or pre-pubescen* or pre-pubert* or pre-adolescen*).ti,ab,kf,dq.

21 (pediat* or paediat* or child* or adolescen* or juvenile*).jx.

22 or/19-21

23 and/13,18,22

24 23 not (conference review or conference abstract).pt.

25 24 use oemezd

26 12 or 25

27 remove duplicates from 26

28 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.

29 Randomized Controlled Trial/

30 exp Randomized Controlled Trials as Topic/

31 "Randomized Controlled Trial (topic)"/

32 Controlled Clinical Trial/

33 exp Controlled Clinical Trials as Topic/

34 "Controlled Clinical Trial (topic)"/

35 Randomization/

36 Random Allocation/

37 Double-Blind Method/

38 Double Blind Procedure/

39 Double-Blind Studies/

40 Single-Blind Method/

41 Single Blind Procedure/

42 Single-Blind Studies/

43 Placebos/

44 Placebo/

45 Control Groups/

46 Control Group/

47 (random* or sham or placebo*).ti,ab,hw,kf.

48 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.

49 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.

50 (control* adj3 (study or studies or trial* or group*)).ti,ab,kf.

51 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.

52 allocated.ti,ab,hw.

53 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.

54 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.

55 (pragmatic study or pragmatic studies).ti,ab,hw,kf.

56 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.

57 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.

58 (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.

59 or/28-58

60 and/1,6,59

61 60 use medall

62 and/13,18,59

63 62 not (conference review or conference abstract).pt.

64 63 use oemezd

65 61 or 64

66 remove duplicates from 65

67 27 or 66

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search terms -- Blincyto OR blinatumomab OR MT-103 OR MT103 OR AMG-103 OR AMG103 OR MEDI-538 OR medi0382 | Child (birth - 17)]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.

[Search terms -- Blincyto OR blinatumomab OR MT-103 OR MT103 OR AMG-103 OR AMG103 OR MEDI-538 OR medi0382]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- Blincyto OR blinatumomab OR MT103 OR AMG103 OR MEDI538]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- Blincyto OR blinatumomab OR MT-103 OR MT103 OR AMG-103 OR AMG103 OR MEDI-538 OR medi0382]

EU Clinical Trials Information System (CTIS)

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- Blincyto OR blinatumomab OR MT-103 OR MT103 OR AMG-103 OR AMG103 OR MEDI-538 OR medi0382]

Grey Literature

Search dates: June 26, 2024 – July 8, 2024

Keywords: blinatumomab, Blincyto, B-ALL, B-Cell, leukaemia, leukemia, lymphoblastic, lymphoma

Limits: none

Relevant websites from the following sections of the grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search

Table 3. Excluded Studies

Study	Reason for exclusion
Studies excluded from the systematic review	
Locatelli, F., et al. (2020). "Blinatumomab versus historical standard therapy in pediatric patients with relapsed/refractory Ph-negative B-cell precursor acute lymphoblastic leukemia." Leukemia 34(9): 2473-2478.	Study design
Gunther, M. (2021). "Blinatumomab for the treatment of children with relapse of B-cell acute lymphoblastic leukemia. [German]." Krankenhauspharmazie 42(7): 327-328.	Study design
Fuster, J. L., et al. (2021). "Blinatumomab to improve the outcome of children with relapsed B-cell acute lymphoblastic leukemia." Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico 23(9): 1963-1966.	Study design
Coppin, R. and A. Leruste (2022). "[Blinatumomab as monotherapy in consolidation treatment after first relapse of Ph-CD19+ ALL in children over one year old]." Bulletin du Cancer 109(4): 391-392.	Study design
Gibson, A., et al. (2024). "Combination low-intensity chemotherapy plus inotuzumab ozogamicin, blinatumomab and rituximab for pediatric patients with relapsed/refractory B-cell acute lymphoblastic leukemia." Haematologica 23: 23.	Population

Appendix 3: Methods of the Studies Included in the Systematic Review

Table 4: Risk Definitions Used in the Included Studies

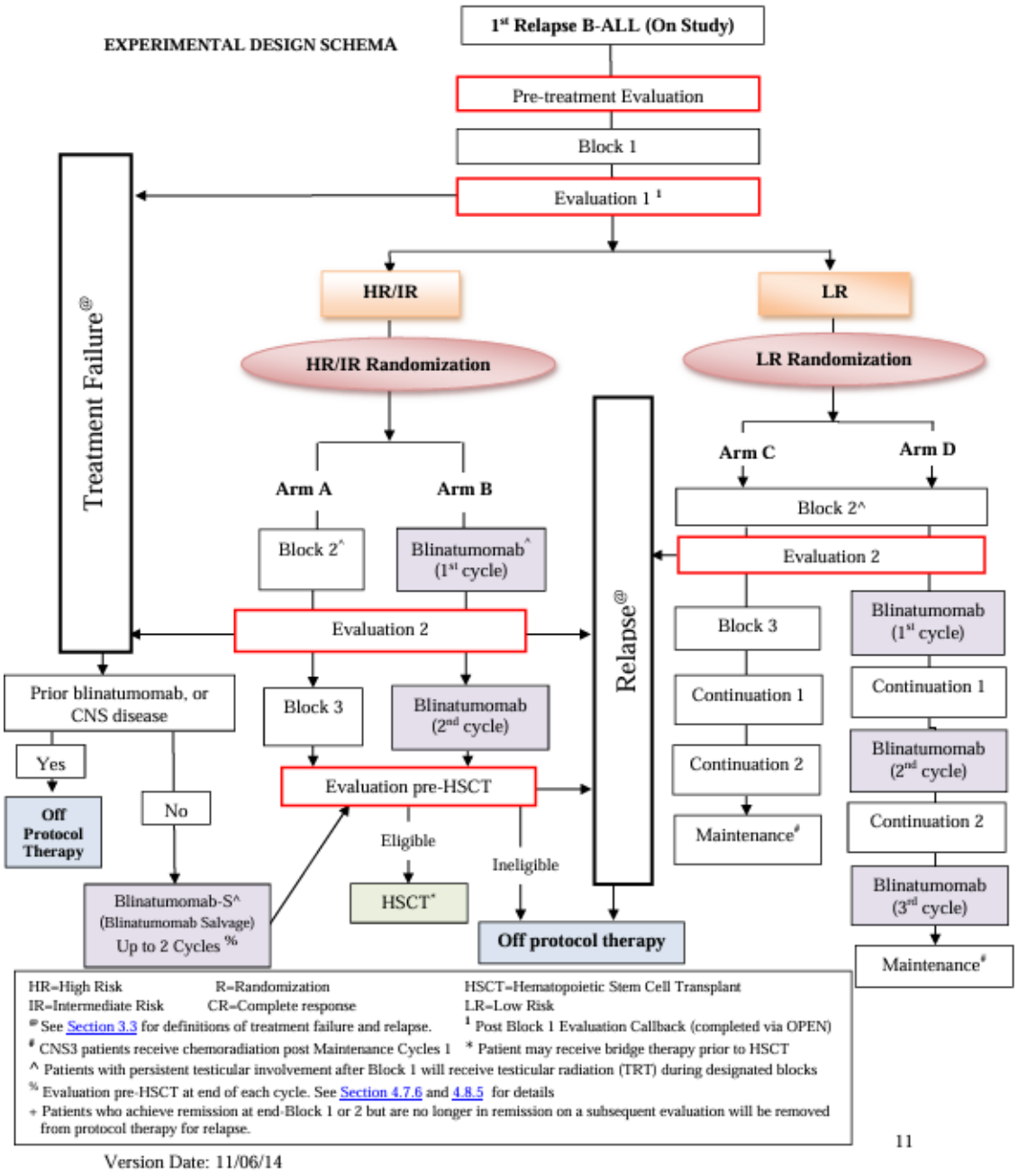
	Locatelli et al. (2021)	COGAALL1331
Risk Stratification Criteria	IntReALL and Berlin-Frankfurt-Münster	Children's Oncology Group
High Risk	○ Very Early Bone Marrow Relapse: Occurs less than 18 months after primary diagnosis. ○ Combined Bone Marrow and Extramedullary Relapse: Relapse involving both the bone marrow (≥25% blasts) and extramedullary sites, regardless of the time from diagnosis. ○ Isolated Extramedullary Relapse: Occurs within 18 months of diagnosis, with or without bone marrow involvement (if bone marrow blasts <5%).	○ Bone Marrow Relapse less than 36 months from initial diagnosis. ○ Isolated Extramedullary Relapse (IEM) less than 18 months after diagnosis.

	Locatelli et al. (2021)	COGAALL1331
Standard or Intermediate Risk	○ Early Bone Marrow Relapse: Occurs 18 months or more after primary diagnosis but less than 6 months after completing therapy, with MRD status not a primary criterion. ○ Isolated Extramedullary Relapse: Occurs between 18 months and 6 months post-therapy.	○ Bone Marrow Relapse more than 36 months from diagnosis with MRD ≥ 0.1% after reinduction therapy. ○ Isolated Extramedullary Relapse more than 18 months from diagnosis, with MRD ≥ 0.1% after reinduction therapy.
Low Risk	○ Relapse occurs 6 months or more after the completion of therapy, whether isolated to bone marrow or extramedullary, and considered less severe due to the longer time since diagnosis.	○ Bone Marrow Relapse more than 36 months after diagnosis and MRD < 0.1% after reinduction therapy. ○ Isolated Extramedullary Relapse more than 18 months after diagnosis and MRD < 0.1%.

IntReALL = International study for treatment of childhood relapsed ALL; MRD = minimal residual disease

Source: Locatelli et al. (2021)[2], Brown et al. (2021)[3], Hogan et al. (2023)[4]

Figure 1: COGAALL1331 Study Design



Source: 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;41(25):4118-4129.[4] "The Creative Commons license does not apply to this content. Use of the material in any format is prohibited without written permission from the publisher, Wolters Kluwer Health, Inc. Please contact permissions@lww.com for further information."

Table 5: Consolidation chemotherapy regimen used in Locatelli et al. (2021)

Drug	Dose	First Block of Consolidation Chemotherapy[a]	Second Block of Consolidation Chemotherapy[a]	Third Block of Consolidation Chemotherapy[a]
Dexamethasone	10 mg/m^2/day	2 doses on days 1-6	2 doses on days 1-6	2 doses on days 1-6
Vincristine	1.5 mg/m^2/day	Days 1 and 6	-	Days 1 and 6
ARA-C	2 g/m^2/dose	2 doses on day 5 of week 5	Days 1-3	-
Methotrexate	1 g/m^2/dose	Over 36 hours, starting on day 1	-	36 hours starting on day 1
Cyclophosphamide	200 mg/m^2/dose	Every 12 hours on days 2-4 (5 doses total)	-	-
PEG-asparaginase	1000 u/m^2	Day 6	Day 6	Day 6
Etoposide	100 mg/m^2/dose	-	Every 12 hours on days 3-5 (5 doses total)	-
Danorubicin	30 mg/m^2	-	-	24-hour continuous infusion starting on Day 5
Ifosfamide	800 mg/m^2/dose	-	-	Every 12 hours on days 2-4 (5 doses total)
Methotrexate	Age-adapted IT	Day 2	Day 1	Day 2
Cytarabine	Age-adapted IT	Day 2	Day 1	Day 2
Prednisolone	Age-adapted IT	Day 2	Day 1	Day 2

ARA-C = cytarabine; IT = intrathecal

a Two weeks is the minimum interval between consolidation chemotherapy blocks. In some cases, this interval may be longer because patients must recover from peripheral cytopenia before starting the next treatment.

Source: Locatelli et al. (2021)[2] Reproduced with permission from [JAMA. 2021;325(9):843-854]. Copyright © (2021) American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Table 6: Reinduction Treatment according to UKALL R3 Protocol[a] and used in COG AALL11331

Drug	Dose	Days
Mitoxantrone	10 mg/m^2/dose	1, 2
Dexamethasone	10 mg/m^2/dose twice daily	1-5, 15-19
Vincristine	1.5 mg/m^2/dose (max 2mg)	1, 8, 15, 22
Pegaspargase[b]	2500 IU/m^2/dose	3, 17
Methotrexate for all patients	Age-based	1
Methotrexate for CNS1[c] only	Age-based IT	8
Methotrexate for CNS2[c] only	Age-based IT	8, (15, 22)[e]
Tripe IT[d] for CNS3[c] and isolated CNS relapse only	Age-based IT	8, 15, 22

CNS = central nervous system; IT = intrathecal

a Administered as a single 4-week course.

b For hypersensitivity, 6 injections of asparaginase Erwinia chrysanthemi may be substituted for each dose of pegaspargase.

c CNS1: CSF WBC < 5 per microliter, no blasts on cytospin; CNS2: CSF WBC < 5 per microliter, blastspresent on cytospin; CNS3: CSF WBC 2 5 per microliter, blasts present on cytospin, or clinical/radiographic signs of central nervous leukemia

d Triple Intrathecal therapy (Triple IT): methotrexate, hydrocortisone, and cytarabine

e Methotrexate dose for Days 15 and 22 onlv for CNS2 subjects who do not have clear CSF samples in weeks 1 & 2.

Source: Brown et al. (2021)[3] Reproduced with permission from [JAMA. 2021;325(9):833-842]. Copyright © (2021) American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Table 7: Consolidation Chemotherapy Schedule in the COGAALL1331 Intermediate- and High-Risk Group

Block 2 (4 weeks)

Drug	Dose	Route	Days
Dexamethasone	3 mg/m^2/dose twice daily	PO or IV	1 - 5
Vincristine	1.5 mg/m^2/dose (max 2mg)	IV	1
Methotrexate for CNS1/2 ONLY	Age-based	IT	8
Triple IT for CNS3 and isolated CNS relapse ONLY[a]	Age-based	IT	8, 22
Methotrexate	1000 mg/m^2/dose	IV over 36 hours	8
Leucovorin	15 mg/m^2/dose every 6 hours	IV or PO	10, 11
Pegaspargase[b]	2500 IU/m^2/dose	IV	9 or 10
Cyclophosphamide	440 mg/m^2/dose	IV	15 - 19
Etoposide	100 mg/m^2/dose	IV	15 - 19

[a] Triple Intrathecal therapy (Triple IT) is made up of methotrexate, hydrocortisone, and cytarabine

[b] For hypersensitivity, 6 injections of asparaginase Erwinia chrysanthemi may be substituted for each dose of pegaspargase

Block 3 (4 weeks)

Drug	Dose	Route	Days
Dexamethasone	3 mg/m^2/dose twice daily	PO or IV	1 - 5
Vincristine	1.5 mg/m^2/dose (max 2mg)	IV	1
Cytarabine	1000 mg/m^2/dose every 12 hours	IV over 3 hours	1, 2, 8, 9
Asparaginase Erwinia	25,000 IU/m^2/dose	IM or IV	2, 4, 9, 11, 23
Methotrexate	1000 mg/m^2/dose	IV over 36 hours	8
Leucovorin	15 mg/m^2/dose every 6 hours	IV or PO	10, 11
Methotrexate for all patients	Age-based	IT	1
Methotrexate for CNS1/2 ONLY	Age-based	IT	22
Triple IT for CNS3 and isolated CNS relapse ONLY[a]	Age-based	IT	22

[a] Triple Intrathecal therapy (Triple IT) is made up of methotrexate, hydrocortisone, and cytarabine.

CNS = central nervous system; IT = intrathecal

Source: Brown et al. (2021)[3] Reproduced with permission from [JAMA. 2021;325(9):833-842]. Copyright © (2021) American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Table 8: Postreinduction Chemotherapy Schedule in the COGAALL1331 Low-Risk Group

Drug	Dose	Days[a]
Block 2		
Dexamethasone	3 mg/m²/dose twice daily	1-5
Vincristine	1.5 mg/m²/dose (max 2 mg)	1
IV methotrexate	1,000 mg/m²/dose	8
Leucovorin	15 mg/m²/dose	10, 11
IT methotrexate	Age-based dosing	8 for CNS1/2
Triple IT	Age-based dosing	8, 22 for CNS3
Pegaspargase	2,500 IU/m²/dose	9 or 10
Cyclophosphamide	440 mg/m²/dose	15-19
Etoposide	100 mg/m²/dose	15-19
Testicular radiation[b]	2,400 cGy in 12 fractions	
Block 3		
Dexamethasone	3 mg/m²/dose twice daily	1-5
Vincristine	1.5 mg/m²/dose (max 2 mg)	1
Cytarabine	3,000 mg/m²/dose every 12 hours	1, 2, 8, 9
Erwinia asparaginase	25,000 IU/m²/dose	2, 4, 9, 11, 23
IT methotrexate	Age-based dosing	1—all patients, 22—CNS1/2
Triple IT	Age-based dosing	22—CNS3
IV methotrexate	1,000 mg/m²/dose	22
Leucovorin	15 mg/m²/dose	24, 25
Continuation 1/2		
Dexamethasone	3 mg/m²/dose twice daily	1-5
Vincristine	1.5 mg/m²/dose (max 2 mg)	1
IT methotrexate	Age-based dosing	1, 43 for CNS1/2
Triple IT	Age-based dosing	1, 43 for CNS3
Mercaptopurine	75 mg/m²/dose	1-42
PO methotrexate	20 mg/m²/dose	8, 15, 29, 36
PO methotrexate	25 mg/m²/dose every 6 hours × 4	22—CNS1/2
Leucovorin	10 mg/m²/dose × 2	24—CNS1/2
IV methotrexate	1,000 mg/m²/dose	22—CNS3
Leucovorin	15 mg/m²/dose	24, 25—CNS3
Cyclophosphamide	300 mg/m²/dose	43, 50
Etoposide	150 mg/m²/dose	43, 50
Thioguanine	40 mg/m²/dose	43-49
Cytarabine	50 mg/m²/dose	44-47, 51-54
Maintenance		
Dexamethasone	3 mg/m²/dose twice daily	1-5, 29-33, 57-61
Vincristine	1.5 mg/m²/dose (max 2 mg)	1, 29, 57
Mercaptopurine	75 mg/m²/dose	1-84
IT methotrexate	Age-based dosing	1 for CNS1/2
Triple IT	Age-based dosing	1 for CNS3[c]
Methotrexate	20 mg/m²/dose weekly	8-78
	(continued in next column)	

Drug	Dose	Days[a]
Chemoradiation-CNS3		
Cranial radiation	1,800 cGy in 10 fractions	
Dexamethasone	5 mg/m²/dose twice daily	1-7, 15-21
Vincristine	1.5 mg/m²/dose (max 2 mg)	1, 8, 15
Pegaspargase	2,500 IU/m²/d	1
Blinatumomab block 1		
Blinatumomab	15 µg/m²/d	1-28
Dexamethasone	5 mg/m²/dose × 1	1
IT methotrexate	Age-based dosing	8, 29 for CNS1/2
Triple IT	Age-based dosing	8, 29 for CNS3
Blinatumomab block 2/3		
Blinatumomab	15 µg/m²/d	1-28

Abbreviations: IT, intrathecal; IV, intravenous; triple IT, methotrexate, cytarabine, hydrocortisone.
[a]Once daily on indicated days unless otherwise specified.
[b]Patients with persistent testicular leukemia at the end of block 1.
[c]CNS3 patients who get cranial radiation get IT therapy during maintenance cycle 1 only.

Source: 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;41(25):4118-4129.[4] "The Creative Commons license does not apply to this content. Use of the material in any format is prohibited without written permission from the publisher, Wolters Kluwer Health, Inc. Please contact permissions@lww.com for further information."Appendix 4: Results of the Studies Included in the Systematic Review

Table 9: COGALL1331 Low-Risk Subgroup Analysis by Disease Site

Variable	COG AALL1331	
	Blinatumomab N = 127	Chemotherapy N = 128
Primary end point[a]: Disease-free survival		
4-year DFS rate, %	61.2 ± 5.0	49.5 ± 5.2
HR (95% CI)[b]; p-value[c]	0.76 (0.51 to 1.14); p=0.89	
BM ± EM	N=87	N=87
4-year DFS rate, %	72.7 ± 5.8	53.7 ± 6.7
HR (95% CI)[b]; p-value[c]	0.53 (0.30 to 0.95); p=0.015	
IEM	N=40	N=41
4-year DFS rate, %	36.6 ± 8.2	38.8 ± 8.0
HR (95% CI); p-value[c]	1.09 (0.62 to 1.93); 0=0.62	
Overall survival		
Follow-up time, median (range)	3.5 years (25 days to 6.6 years)	
4-year OS rate, %	90.4 ± 3.0	79.6 ± 4.3
HR (95% CI)[b]; p-value[c]	0.65 (0.32 to 1.30); p=0.11	
BM ± EM	N = 87	N=87
4-year OS rate, %	97.1 ± 2.1	84.8 ± 4.8
HR (95% CI)[b]; p-value[c]	0.28 (0.08 to 1.02); p=0.020	
IEM	N= 40	N=41
4-year OS rate, %	76.5 ± 7.5	68.8 ± 8.6
HR (95% CI)[b]; p-value[c]	1.04 (0.43 to 2.50); p=0.53	

CI = confidence interval; BM = bone marrow; DFS = disease-free survival; EM = extramedullary; HR = hazard ratio; IEM = isolated extramedullary; OS = overall survival

a The primary end point was disease-free survival defined as time from randomization to relapse, second malignancy, or death.

b Based on a stratified Cox proportional hazards regression model that was tested using graphical diagnostics and verified based on scaled Schoenfeld residuals.

c P value has not been adjusted for multiple testing so there is risk of type I error.

Source: Hogan et al. (2023)[4]

Appendix 5: Place in Therapy

Contents within this section have been informed by input from the clinical expert(s) consulted for the purpose of this review and from clinician groups. The following has been summarized by the review team.

Potential Place in Therapy

The clinical experts emphasized that blinatumomab, with its novel mechanism of targeting CD19+ cells, complements existing treatments and has become a new standard of care for pediatric patients with Ph-negative B-acute lymphoblastic leukemia (B-ALL) in first relapse in Canada. It has been incorporated into treatment protocols due to its ability to improve disease-free survival (DFS), event-free survival (EFS), overall survival (OS), and minimal residual disease (MRD) clearance, while reducing severe toxicities compared to traditional chemotherapy. Blinatumomab's use, independent of chemotherapy cycles, allows more patients to proceed to curative hematopoietic stem cell transplantation with fewer life-threatening side effects, filling an unmet need for patients with incomplete responses to chemotherapy and high toxicity risks. Results from recently published trials further support its effectiveness, shifting clinical practice away from intensive chemotherapy alone. The experts also noted that emerging data and interim results from the COGAALL1371 study strongly supports the inclusion of blinatumomab as a first-line treatment option across most subsets of pediatric B-ALL patients, except for those classified as Standard-Risk Favorable.

Input from the clinician group aligns with the clinical experts view that blinatumomab has shifted the treatment paradigm for pediatric B-ALL, becoming a preferred option due to its efficacy and reduced toxicity. Both emphasize its role in improving disease control and its adoption as a standard of care. The clinician group emphasized the role of blinatumomab in replacing less tolerated chemotherapy blocks and improving outcomes in patients with bone marrow involvement. The clinician group also requested that CDA-AMC consider expanding the scope of the review, which initially only included low risk patients, to include the high- and intermediate-risk cohorts as well.

Patient Population

The clinical experts suggest that while blinatumomab is effective for most patients with B-ALL, it may not offer additional benefit for pediatric patients with the most favorable risk characteristics (Standard-Risk Favorable), who already achieve excellent outcomes (5-year EFS of 96-97% and 5-year OS of 99-100%) with standard chemotherapy alone. However, emerging data from trials (COG AALL1732 and E1910) support its use in other pediatric ALL subsets, recommending two non-sequential courses of post-induction blinatumomab. Blinatumomab is especially beneficial for patients with marrow or combined marrow-extramedullary disease. Additionally, in patients previously treated with CD19-targeted therapies (e.g., CAR T cell therapy), CD19 expression should be reassessed before using blinatumomab, as it is ineffective in CD19-negative disease, though this phenomenon primarily occurs after CD19-targeted treatments.

The clinician group largely agrees with the experts but highlights an important exception: patients with low-risk isolated extramedullary disease, particularly isolated CNS relapse, do not benefit from blinatumomab due to its poor CNS penetration. For these patients, older protocols with high-dose cytarabine and methotrexate may be more effective.

Assessing the Response Treatment

The clinical experts note that treatment response would be typically assessed through bone marrow biopsy and MRD testing using flow cytometry or next-generation sequencing, and, if needed, assessment of extramedullary sites. Response is monitored at the end of induction and throughout subsequent cycles, particularly through MRD evaluation and extramedullary site assessment if necessary. The clinician group agrees that monitoring response through bone marrow and peripheral blood counts is standard but emphasized that for patients undergoing MRD assessment by flow cytometry after blinatumomab, a non-CD19 dependent methodology should be employed.

Discontinuing Treatment

The clinical experts and clinician group agree that treatment discontinuation should be considered for several reasons: the development of Grade 4 or higher blinatumomab-related toxicities that do not resolve with drug holds, persistent CRS and/or CNS toxicity despite dose adjustments and corticosteroid use, and lack of treatment response or relapse during or after therapy. In such cases, patients should discontinue blinatumomab and pursue alternative potentially curative therapies, such as CAR T-cell therapy or HSCT.

Prescribing Considerations

Both clinical experts and the clinician group emphasize that pediatric patients receiving blinatumomab must be diagnosed, treated, and monitored by a pediatric oncologist. Blinatumomab therapy should be initiated at specialized pediatric oncology centers. However, once the patient is stable and tolerates the infusion, routine tasks like 'bag changes' for the continuous infusion can be managed at community hospitals or clinics, provided proper training and reimbursement arrangements are in place.

Additional Considerations

The clinician group expressed that future reimbursement strategies for blinatumomab must address drug wastage, which occurs through three main mechanisms: extra drug needed to prime the infusion line, leftover vial contents after preparing pediatric doses (currently unreimbursed), and drug loss from unplanned infusion interruptions (e.g., pump failure or pauses for toxicity). Comprehensive reimbursement that accounts for these forms of wastage is essential to ensure equitable access to blinatumomab across different regions.

The clinical experts emphasized that Philadelphia-positive B-ALL patients at first relapse should be eligible for the treatment with blinatumomab, noting that in the adult population, where Ph-positive cases are more common, blinatumomab is considered a standard of care. As per the experts, there is no biological reason to believe Ph-positive patients would respond differently to treatment with blinatumomab compared to Ph-negative patients.

The clinical experts and the clinician group have highlighted that the Children's Oncology Group is conducting a phase III randomized controlled trial to evaluate the efficacy of blinatumomab in combination with chemotherapy for patients aged 1 to 10 years with newly diagnosed, standard-risk B-lymphoblastic leukemia or B-lymphoblastic lymphoma, with or without Down syndrome. The clinicians expressed strong support for the use of blinatumomab in the first-line setting based on interim efficacy results from the COGAALL1731 trial. They emphasized that emerging data from this trial strongly supports the inclusion of blinatumomab as part of first-line therapy across most subsets of the pediatric B-ALL population, except for those classified as Standard-Risk Favorable. As this trial did not meet the eligibility criteria for the systematic review, its results were not summarized or appraised herein. As such, the CDA-AMC review team cannot comment on the certainty of evidence or clinical relevance of the results for any end point assessed.

Additionally, Amgen has provided advance notification of its intent to submit blinatumomab (Blincyto) for CDA-AMC review for use in Philadelphia chromosome-negative, CD19-positive B-cell precursor acute lymphoblastic leukemia during the consolidation phase of multiphase chemotherapy, with an anticipated submission date of October 18, 2024.

Economic Review Appendices

Appendix 6: Cost Comparison Table

The comparators presented in Table and Table have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on two published studies on the COG AALL 1331 trial and validated by clinical experts.[3,4] If discrepancies in dosing between the monograph and Canadian clinical practice exist, the dose specified by clinical experts was used. Pricing for comparator products was based on publicly available list prices from IQVIA Delta PA Database, Ontario Drug Benefit formulary, British Columbia Pharmacare formulary and published CADTH review of Rylaze.[5-8]

Blinatumomab is intercalated with chemotherapy blocks, replacing or supplementing specific chemotherapy blocks, in LR and IR/HR patients.[3,4] According to clinical expert feedback, block 1 chemotherapy stratifies patients into LR and IR/HR subgroups based on response to treatment. In LR patients, blinatumomab is integrated into the chemotherapy regimen in a phased manner. All LR patients are expected to receive block 1 and block 2 chemotherapy. The first cycle of blinatumomab replaces the block 3 chemotherapy. Following this, two additional cycles of blinatumomab are administered between two cycles of continuation chemotherapy and between the second cycle of continuation and first cycle of maintenance chemotherapy. This results in extending the treatment duration of patients by 10 weeks. In IR/HR patients, two cycles of blinatumomab replace block 2 and block 3 of

chemotherapy. Because each blinatumomab cycle is 5 weeks long and each chemotherapy block is 4 weeks, blinatumomab extends treatment course by 2 weeks.

The recommended dose of blinatumomab is 15 mcg/m^2/day (maximum 28 mcg/day) continuous IV infusion, followed by 7-day break (Table 10 and Table). At $2,978.26 per vial,[5] the treatment acquisition cost of blinatumomab is $2,978.26 to $5,879.16 daily, or $83,391 to $164,617 per patient per treatment course (the upper range representing the cost of a maximum dose). Blinatumomab is expected to cost $225,282 to $468,959 more per patient in LR patients over the treatment course, compared to chemotherapy (Table). Because all LR patients are expected to receive block 1 and block 2 chemotherapy, irrespective of blinatumomab, no cost differences in treatments preceding blinatumomab administration are anticipated. In IR/HR patients, blinatumomab is expected to cost $135,299 to $302,083 more per patient compared to chemotherapy over the course of the treatment (Table). Results may differ by jurisdiction depending on individual list prices for the drugs under review compared to those presented in Table and Table .

Table 10: CDA-AMC Cost Comparison Table for Pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor (ALL) – low-risk patients

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
Blinatumomab (Blincyto)	**38.5 mcg vial**	**Lyophilized powder for solution for infusion**	**$2,978.2599[b]**	**Cycle 1, 2 and 3 Day 1-28: 15 mcg/m^2/day (maximum 28 mcg/day) continuous IV infusion, followed by 7-day break[c]**	**$2,978.26 to $5,879.16**	**$83,391 to $164,617**
Blinatumomab cycle 1 (5 weeks) Day 1-28: 15 mcg/m^2/day (maximum 28 mcg/day) of blinatumomab Day 1-5: 3 mg/m^2/dose twice daily of dexamethasone For CNS 1, CNS 2 patients Day 9, 29: age-based intrathecal methotrexate For CNS 3 patients Days 9, 29: age-based triple intrathecal therapy (cytarabine, hydrocortisone, methotrexate)					$2,388.37 to $4,709.14 For CNS 1, CNS 2 patients $2,388.88 to $4,709.65 For CNS 3 patients $2,393.59 to $4,714.35	$83,593 to $164,820 For CNS 1, CNS 2 patients $83,611to $164,838 For CNS 3 patients $83,776 to $165,002
Blinatumomab cycle 2 (5 weeks) Day 1-28: 15 mcg/m^2/day (max 28 mcg/day) of blinatumomab					$2,382.61 to $4,703.33	$83,391 to $164,617
Blinatumomab cycle 3 (5 weeks) Day 1-28: 15 mcg/m^2/day (max 28 mcg/day) of blinatumomab					$2,382.61 to $4,703.33	$83,391 to $164,617
Blinatumomab cycle 1, 2 and 3						$250,376 to $494,053
Blinatumomab cycle 1, followed by continuous 1 chemotherapy, blinatumomab cycle 2, continuous 2 chemotherapy, blinatumomab cycle 3, followed by two cycles of maintenance chemotherapy						$256,159 to $499,837
Chemotherapy						
Cyclophosphamide (Procytox)	200 mg 500 mg 1000 mg 2000 mg vial	Powder for injection	$74.2300[d] $107.8100 $195.4200 $359.4000	Continuation 1, Continuation 2 Days 43, 50: 300 mg/m^2/dose	Continuation 1, Continuation 2 $107.81	Continuation 1, Continuation 2 $216

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
Cytarabine (Cytosar)	100 mg 500 mg 1,000 mg 2,000 mg Vial	Lyophilized powder for injection	Not available $76.8500[b] Not available $306.5000[b]	Block 3 Day 1, 2, 8, 9: 3,000 mg/m²/dose every 12 hours For CNS 3 patients	Block 3 $689.85 For CNS 3 patients $76.85	Block 3 $2,759 For CNS 3 patients $77
	100 mg/5 mL 500 mg/25 mL 1000 mg/10 mL 2000 mg/20 mL Vial	Solution for injection		Day 22: age-based dosing (16 mg to 30 mg) of intrathecal cytarabine as part of triple intrathecal therapy[e] Cycle 1 For CNS 3 patients	Cycle 1 For CNS 3 patients $76.85	Cycle 1 For CNS 3 patients $154
				Day 9, 29: age-based dosing (16 mg to 30 mg) of intrathecal cytarabine as part of triple intrathecal therapy[e,f] Continuation 1, Continuation 2 Days 44–47, 51–54: 50 mg/m²/dose For CNS 3 patients	Continuation 1, Continuation 2 $76.85 For CNS 3 patients $76.85	Continuation 1, Continuation 2 $615 For CNS 3 patients $77
				Day 1, 43: age-based dosing (16 mg to 30 mg) of intrathecal cytarabine as part of triple intrathecal therapy[e] Maintenance For CNS 3 patients	Maintenance For CNS 3 patients $76.85	Maintenance For CNS 3 patients $77
				Days 1: age-based dosing (16 mg to 30 mg) of intrathecal cytarabine as part of triple intrathecal therapy[e]		
Dexamethasone (generic)	0.5 mg 4 mg	Tablet	$0.1564 $0.6112	Block 3, Continuation 1, Continuation 2	Block 3, Continuation 1, Continuation 2	Block 3, Continuation 1, Continuation 2

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
				Day 1-5: 3 mg/m^2/dose twice daily Cycle 1 Day 1: 5 mg/m^2/dose (maximum 20 mg/dose) prior to starting blinatumomab infusion Maintenance Day 1-5, 29-33, 57-61: 3 mg/m^2/dose twice daily	$1.54 Cycle 1 $1.55 to $3.06 Maintenance $1.54	$8 Cycle 1 $2 to $3 Maintenance $23
Erwinia asparaginase (Erwinase)	10,000 IU/ 3 mL Vial	Freeze-dried powder for injection	$1,091.9100[g,h]	Block 3 Day 2, 4, 9, 11, 23: 25,000 IU/m^2/dose	$4,367.64	$21,838
Etoposide (generic)	100 mg/5 mL 200 mg/10 mL 500 mg/25 mL 1,000 mg/50 mL Vial	Solution for injection or infusion	$75.0000[b] $150.0000[b] $375.0000[b] $750.0000[b]	Continuation 1, Continuation 2 Days 43, 50: 150 mg/m^2/dose IV	Continuation 1, Continuation 2 $225.00	Continuation 1, Continuation 2 $450
Hydrocortisone (Solu-cortef)	100 mg 250 mg 500 mg 1,000 mg Vial	Sterile powder and diluent	$5.4440[i] $9.2059[i] $19.0296[i] $35.4309[i]	Block 3 For CNS 3 patients Day 22: age-based dosing (8 mg to 15 mg) of intrathecal hydrocortisone as part of triple intrathecal therapy[e] Cycle 1 For CNS 3 patients Day 9, 29: age-based dosing (8 mg to 15 mg) of intrathecal hydrocortisone as part of triple intrathecal therapy[e,f] Continuation 1, Continuation 2	Block 3, Maintenance $5.44 Cycle 1, Continuation 1, Continuation 2 For CNS 3 patients $5.44	Block 3, Maintenance $5 Cycle 1, Continuation 1, Continuation 2 For CNS 3 patients $11

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
				For CNS 3 patients Day 1, 43: age-based dosing (8 mg to 15 mg) of intrathecal hydrocortisone as part of triple intrathecal therapy[e] Maintenance For CNS 3 patients Day 1: age-based dosing (8 mg to 15 mg) of intrathecal hydrocortisone as part of triple intrathecal therapy[e]		
Leucovorin (generic)	50 mg/5 mL 500 mg/50 mL Vial	Solution for Injection, Intramuscular Injection or Intravenous use	$68.9400[b] $689.0000[b]	Block 3 Day 24, 25: 15 mg/m²/dose Continuation 1, Continuation 2 For CNS 3 patients Days 24, 25: 15 mg/m²/dose IV[i]	Block 3 $68.94 Continuation 1, Continuation 2 For CNS 3 patients $68.94	Block 3 $138 Continuation 1, Continuation 2 For CNS 3 patients $138
Leucovorin (generic)	5 mg	Tablet	$3.6776	Continuation 1, Continuation 2 For CNS 1, CNS 2 patients Day 24: 10 mg/m²/dose for 2 doses orally[i]	Continuation 1, Continuation 2 For CNS 1, CNS 2 patients $22.07	Continuation 1, Continuation 2 For CNS 1, CNS 2 patients $22
Mercaptopurine (generic, purinethol)	50 mg	Tablet	$2.8610	Continuation 1, Continuation 2 Day 1-42: 75 mg/m²/dose once daily Maintenance Days 1–84: 75 mg/m²/dose once daily	Continuation 1, Continuation 2 $8.58 Maintenance $8.58	Continuation 1, Continuation 2 $360 Maintenance $721
Methotrexate (generic)	20 mg/2 mL 50 mg/2 mL Vial	Solution for intramuscular, intravenous,	$12.5000 $8.9200	Block 3 Day 1: age-based dosing (8 mg to	Block 3 $129.34	Block 3 $259

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
		intraarterial, intrathecal, intracerebroventricular use		15 mg) of intrathecal methotrexate[e] Day 22: 1,000 mg/m^2/dose IV For CNS 1, CNS 2 patients Day 1, 22: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate[e] For CNS 3 patients Day 22: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate as part of triple intrathecal therapy[e] Cycle 1 For CNS 1, CNS 2 patients Day 9, 29: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate[e,f] For CNS 3 patients Day 9, 29: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate as part of triple intrathecal therapy[e,f] Continuation 1, Continuation 2 For CNS 1, CNS 2 patients Day 1, 43: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate[e] For CNS 3 patients	For CNS 1, CNS 2 patients $8.92 For CNS 3 patients $8.92 Cycle 1 For CNS 1, CNS 2 and CNS 3 patients $8.92 Continuation 1, Continuation 2 For CNS 1, CNS 2 patients $8.92 For CNS 3 patients $133.80 Maintenance For CNS 1, CNS 2 and CNS 3 patients $8.92	For CNS 1, CNS 2 patients $18 For CNS 3 patients $9 Cycle 1 For CNS 1, CNS 2 and CNS 3 patients $18 Continuation 1, Continuation 2 For CNS 1, CNS 2 patients $18 For CNS 3 patients $268 Maintenance For CNS 1, CNS 2 and CNS 3 patients $9

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
				Day 22: 1,000 mg/m^2/dose IV[k] Day 1, 43: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate as part of triple intrathecal therapy[e] Maintenance For CNS 1, CNS 2 patients Day 1: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate[e] For CNS 3 patients Day 1: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate as part of triple intrathecal therapy[e]		
Methotrexate (generic)	2.5 mg	Tablet	$0.2513	Continuation 1, Continuation 2 Day 8, 15, 29, 36: 20 mg/m^2/dose orally[k] For CNS 1,2 patients Day 22: 25 mg/m^2/dose every 6 hours for 4 doses orally[k] Maintenance Day 8-78: 20 mg/m^2/dose weekly orally[k]	Continuation 1, Continuation 2 $3.02 For CNS 1,2 patients $14.07 Maintenance $3.02	Continuation 1, Continuation 2 $12 For CNS 1,2 patients $14 Maintenance $33
Thioguanine (Lanvis)	40 mg	Tablet	$6.2030	Continuation 1, Continuation 2 Days 43-49: 40 mg/m^2/dose once daily	Continuation 1, Continuation 2 $12.41	Continuation 1, Continuation 2 $87

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
Vincristine (generic)	1 mg/mL Vial	Solution for infusion	$30.6000	Block 3, Continuation 1, Continuation 2 Day 1: 1.5 mg/m^2/dose (maximum 2 mg) Maintenance Day 1, 29, 57: 1.5 mg/m^2/dose (maximum 2 mg)	Block 3, Continuation 1, Continuation 2 $91.80 Maintenance $91.80	Block 3, Continuation 1, Continuation 2 $92 Maintenance $275
Block 3 (4 weeks) Day 1-5: 3 mg/m^2/dose twice daily of dexamethasone Day 1: 1.5 mg/m^2/dose (maximum 2 mg) of vincristine Day 1, 2, 8, 9: 3,000 mg/m^2/dose of cytarabine Day 1: age-based intrathecal methotrexate Day 2, 4, 9, 11, 23: 25,000 IU/m^2/dose of erwinia asparaginase Day 22: 1,000mg/m^2/dose of IV methotrexate Day 24, 25: 15 mg/m^2/dose of leucovorin For CNS 1, CNS 2 patients Day 1, 22: age-based intrathecal methotrexate For CNS 3 patients Days 22: age-based intrathecal triple intrathecal therapy (cytarabine, hydrocortisone, methotrexate)					$896.20 For CNS 1, CNS 2 patients $896.84 For CNS 3 patients $899.46	$25,094 For CNS 1, CNS 2 patients $25,111 For CNS 3 patients $25,185
Continuation 1, Continuation 2 (8 weeks) Day 1-5: 3 mg/m^2/dose twice daily of dexamethasone Day 1: 1.5 mg/m^2/dose (maximum 2 mg) of vincristine Day 1-42: 75 mg/m^2/dose of mercaptopurine Days 8, 15, 29, 36: 20 mg/m^2/dose orally of methotrexate Days 43, 50: 300 mg/m^2/dose of cyclophosphamide Days 43, 50: 150 mg/m^2/dose of etoposide Days 43-49: 40 mg/m^2/dose once daily of thioguanine Days 44–47, 51–54: 50 mg/m^2/dose of cytarabine For CNS 1, CNS 2 patients Day 1, 43: age-based intrathecal methotrexate Day 22: 25 mg/m^2/dose every 6 hours for 4 doses orally of methotrexate Day 24: 10 mg/m^2/dose for 2 doses orally of leucovorin For CNS 3 patients Days 1, 43: age-based intrathecal triple intrathecal therapy (cytarabine, hydrocortisone, methotrexate) Day 22: 1,000mg/m^2/dose of IV methotrexate Days 24, 25: 15 mg/m^2/dose IV leucovorin					$32.84 For CNS 1, CNS 2 patients $33.81 For CNS 3 patients $43.02	$1,839 For CNS 1, CNS 2 patients $1,893 For CNS 3 patients $2,409
Maintenance (12 weeks)[l] Day 1-5, 29-33, 57-61: 3 mg/m^2/dose twice daily of dexamethasone Day 1, 29, 57: 1.5 mg/m^2/dose (maximum 2 mg) of vincristine Day 1-84: 75 mg/m^2/dose of mercaptopurine Days 8-78: 20 mg/m^2/dose weekly orally of methotrexate For CNS 1, CNS 2 patients Day 1: age-based intrathecal methotrexate For CNS 3 patients[m] Days 1: age-based intrathecal triple intrathecal therapy (cytarabine, hydrocortisone, methotrexate)[n]					$12.53 For CNS 1, CNS 2 patients $12.64 For CNS 3 patients $13.62	$1,053 For CNS 1, CNS 2 patients $1,061 For CNS 3 patients $1,144

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
Block 3, followed by two cycles of continuous chemotherapy, followed by two cycles of maintenance chemotherapy						$30,877

CNS = central nervous system, IU = international unit, IV = intravenous infusion

Note: Unit prices of medications are taken from the Ontario Drug Benefit Formulary (accessed September 26, 2024),[6] unless otherwise indicated, and do not include dispensing fees. For treatments using weight- or body surface area (BSA) based dosing, CADTH assumed a weight of 45 kg and 1.4m^2. All costs include wastage of unused medication in vials and do not include dispensing fees. Dosing is obtained Hogan et al. 2023,[4] and validated with clinical expert feedback.

Note: Blinatumomab is preceded by block 1 and block 2 of chemotherapy for LR patients. In the study by Hogan et al. 2023,[4] block 1 chemotherapy consisted of 10 mg/m^2/dose twice daily of dexamethasone on day 1-5 and 15-19, 1.5 mg/m^2/dose (maximum 2 mg) of vincristine on day 1, 8, 15 and 22, 2,500 IU/m^2/dose of pegaspargase on day 3 and 17, 10 mg/m^2/dose of mitoxantrone on day 1 and 2. Patients with CNS 1 and CNS 2 received age-based intrathecal methotrexate on day 1 and 8. Patients with CNS 3 additionally received age-based intrathecal triple intrathecal therapy (cytarabine, hydrocortisone, methotrexate) on day 8, 15 and 22. Block 2 chemotherapy consisted of 3 mg/m^2/dose twice daily of dexamethasone on day 1-5, 1.5 mg/m^2/dose (maximum 2 mg) of vincristine on day 1, 1,000 mg/m^2/dose of IV methotrexate on day 8, 15 mg/m^2/dose of leucovorin on day 10 and 11, 2,500 IU/m^2/dose of pegaspargase on day 9 or 10, 440 mg/m^2/dose of cyclophosphamide on day 15-19, 100 mg/m^2/dose of etoposide on day 15-19. Patients with CNS 1 and CNS 2 received age-based intrathecal methotrexate on day 8. Patients with CNS 3 additionally received age-based intrathecal triple intrathecal therapy (cytarabine, hydrocortisone, methotrexate) on day 8 and 22. Patients with persistent testicular leukemia also received 2,400 cGy of testicular radiation in 12 fractions at the end of block 1 chemotherapy. According to clinical expert feedback, block 1 chemotherapy stratifies patients by risk based on treatment response. All LR patients are expected to receive block 1 and block 2 chemotherapy, irrespective of blinatumomab, and hence no cost differences are anticipated. Consequently, costs for block 1 and block 2 chemotherapy are not provided in the cost comparison table.

[a] The average daily cost of each drug was calculated by dividing the treatment cost by the number of days over which the drug is administered. The average daily cost of each cycle or block was determined by dividing the total cycle or block cost by the duration of the cycle or block.

[b] IQVIA Delta PA database,[5] accessed September 9, 2024.

[c] According to the product monograph, blinatumomab IV bag can be changed every 24 hours, 48 hours, 72 hours, 96 hours or 7 days.[9] Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. Supervision by a healthcare professional or hospitalization is recommended for all subsequent cycle starts and reinitiations. Premedication is also recommended with 5 mg/m^2 of dexamethasone, to a maximum dose of 20 mg prior to the first dose of blinatumomab in the first cycle, prior to a step dose (such as Cycle 1 Day 8), or when restarting an infusion after an interruption of 4 or more hours in the first cycle. Intrathecal chemotherapy CNS prophylaxis is recommended before and during blinatumomab therapy to prevent central nervous system ALL relapse. The maximum dose of blinatumomab was informed by clinical expert input.

[d] Expired price is not used in calculation of treatment costs.

[e] Age-based dosing was informed by clinical expert input.

[f] According to clinical expert feedback, intrathecal therapy may be administered at day 9 and 29 in clinical practice. In the study by Hogan et al. 2023,[4] intrathecal therapy was given on day 8 and 29.

[g] CADTH review of Rylaze.[8]

[h] At the time of this review, Erwinase was only available in Canada through exceptional importation and sale (i.e., it is a designated drug). CADTH was unable to independently verify the list price of Erwinase, nor the costs paid by jurisdictional drug plans through exceptional importation.[8] According to clinical experts input, Erwinase supply may be discontinued and replaced with Rylaze but the timeline for this change to take effect is uncertain.

[i] British Columbia pharmacare formulary,[7] accessed September 9, 2024.

[j] According to clinical expert feedback, leucovorin dose is administered intravenously to patients with CNS 3 and orally to patients with CNS 1 and CNS 2.

[k] Methotrexate form of administration, intravenously or orally, is informed by clinical expert input.

[l] Patients receive maintenance chemotherapy until total of 2 years after start of Block 1.[4]

[m] For CNS 3 patients, chemoradiation is given between first and second cycles of maintenance. Maintenance chemoradiation consists of 5 mg/m^2/dose twice daily of dexamethasone on day 1-7 and 15-21, 1.5 mg/m^2/dose (maximum 2 mg) of vincristine on day 1, 8, and 15, 2,500 IU/m^2/dose of pegaspargase on day 1 and 1,800 cGy of cranial radiation in 10 daily fractions of 180 cGy.

[n] Following cycle 2 of maintenance chemotherapy, CNS 3 patients don't receive intrathecal therapy.

Table 11: CDA-AMC Cost Comparison Table for Pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor (ALL) – intermediate and high-risk patients

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
Blinatumomab (Blincyto)	**38.5 mcg vial**	**Lyophilized powder for solution for infusion**	**$2,978.2599[b]**	**Cycle 1 and 2 Day 1-28: 15 mcg/m^2/day (maximum 28 mcg/day) continuous IV infusion, followed by 7-day break[c,d]** **For patient with M2 or M3 marrow, cycle 1 dose may be escalated. Day 1-7: 5 mcg/m^2/day (maximum 9 mcg/day)[c,d]** **Day 8-28: 15 mcg/m^2/day (maximum 28 mcg/day)[c,d]**	**$2,978.26 to $5,956.52** **For patients with M2 or M3 marrow** **$2,978.26 to $5,211.95**	**$83,391 to $166,783** **For patients with M2 or M3 marrow** **$83,391 to $145,935**
Blinatumomab cycle 1 (5 weeks) Day 1-28: 15 mcg/m^2/day (maximum 28 mcg/day) of blinatumomab Day 1: 5 mg/m^2/dose (maximum 20 mg/dose) of dexamethasone For CNS 1, CNS 2 patients Day 17, 29: age-based intrathecal methotrexate For CNS 3 and isolated CNS relapse patients Days 17, 29: age-based intrathecal triple intrathecal therapy (cytarabine, hydrocortisone, methotrexate)					$2,382.65 to $4,765.30 For CNS 1, CNS 2 patients $2,383.16 to $4,765.81 For CNS 3 and isolated CNS relapse patients $2,387.86 to $4,770.52	$83,393 to $166,786 For CNS 1, CNS 2 patients $83,411 to $166,803 For CNS 3 and isolated CNS relapse patients $83,575 to $166,968
Blinatumomab cycle 2 (5 weeks) Day 1-28: 15 mcg/m^2/day (max 28 mcg/day) of blinatumomab For CNS 1, CNS 2 patients Day 9, 29: age-based intrathecal methotrexate For CNS 3 and isolated CNS relapse patients Day 9, 29: age-based intrathecal triple intrathecal therapy (cytarabine, hydrocortisone, methotrexate)					$2,382.61 to $4,765.22 For CNS 1, CNS 2 patients $2,383.12 to $4,765.73 For CNS 3 and isolated CNS relapse patients $2,387.82 to $4,770.43	$83,391 to $166,783 For CNS 1, CNS 2 patients $83,409 to $166,800 For CNS 3 and isolated CNS relapse patients $83,574 to $166,965
Blinatumomab cycle 1 and 2						$166,784 to $333,568
Chemotherapy						

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
Cyclophosphamide (Procytox)	200 mg 500 mg 1000 mg 2000 mg Vial	Powder for injection	$74.2300[b,e] $107.8100[b] $195.4200[b] $359.4000[b]	Block 2 Day 15–19: 440 mg/m²/dose IV	Block 2 $215.62	Block 2 $1,078
Cytarabine (Cytosar)	100 mg 500 mg 1,000 mg 2,000 mg Vial	Lyophilized powder for injection	Not available $76.8500[b] Not available $306.5000[b]	Block 2 For CNS 3 patients and isolated CNS relapse patients Day 8, 22: age-based dosing (16 mg to 30 mg) of intrathecal cytarabine as part of triple intrathecal therapy[f] Block 3 Day 1, 2, 8, 9: 1,000 mg/m²/dose every 12 hours IV over 3 hours For CNS 3 and isolated CNS relapse patients Day 22: age-based dosing (16 mg to 30 mg) of intrathecal cytarabine as part of triple intrathecal therapy[f] Cycle 1 For CNS 3 and isolated CNS relapse patients Day 17, 29: age-based dosing (16 mg to 30 mg) of intrathecal cytarabine as part of triple intrathecal therapy[f,g] Cycle 2 For CNS 3 and isolated CNS relapse patients Day 9, 29: age-based dosing (16 mg to 30 mg) of	Block 2, Cycle 1, Cycle 2 $76.85 Block 3 $230.55 For CNS 3 and isolated CNS relapse patients $76.85	Block 2, Cycle 1, Cycle 2 $154 Block 3 $922 For CNS 3 and isolated CNS relapse patients $77
	100 mg/5 mL 500 mg/25 mL 1000 mg/10 mL 2000 mg/20 mL Vial	Solution for injection				

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
				intrathecal cytarabine as part of triple intrathecal therapy[f,h]		
Dexamethasone (generic)	0.5 mg 4 mg	Tablet	$0.1564 $0.6112	Block 2, Block 3 Day 1–5: 3 mg/m²/dose twice daily Cycle 1 Day 1: 5 mg/m²/dose (maximum 20 mg/dose) prior to starting blinatumomab infusion	Block 2, Block 3 $1.54 Cycle 1 $1.55 to $3.06	Block 2, Block 3 $8 Cycle 1 $2 to $3
Erwinia asparaginase (Erwinase)	10,000 IU/ 3 mL Vial	Freeze-Dried Powder for Injection	$1,091.9100[i,j]	Block 3 Day 2, 4, 9, 11, 23: 25,000 IU/m²/dose IM or IV	Block 3 $4,367.64	Block 3 $21,838
Etoposide (generic)	100 mg/5 mL 200 mg/10 mL 500 mg/25 mL 1,000 mg/50 mL Vial	Solution for injection or infusion	$75.0000[b] $150.0000[b] $375.0000[b] $750.0000[b]	Block 2 Day 15–19: 100 mg/m²/dose IV	Block 2 $150.00	Block 2 $750
Hydrocortisone (Solu-cortef)	100 mg 250 mg 500 mg 1,000 mg Vial	Sterile powder and diluent	$5.4440[k] $9.2059[k] $19.0296[k] $35.4309[k]	Block 2 For CNS 3 patients and isolated CNS relapse patients Days 8, 22: age-based dosing (8 mg to 15 mg) of intrathecal hydrocortisone as part of triple intrathecal therapy[f] Block 3 For CNS 3 and isolated CNS relapse patients Day 22: age-based dosing (8 mg to 15 mg) of intrathecal hydrocortisone as part of triple intrathecal therapy[f]	Block 2, Cycle 1, Cycle 2 $5.44 Block 3 $5.44	Block 2, Cycle 1, Cycle 2 $11 Block 3 $5

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
				Cycle 1 For CNS 3 and isolated CNS relapse patients Day 17, 29: age-based dosing (8 mg to 15 mg) of intrathecal hydrocortisone as part of triple intrathecal therapy[f,g] Cycle 2 For CNS 3 and isolated CNS relapse patients Day 9, 29: age-based dosing (8 mg to 15 mg) of intrathecal hydrocortisone as part of triple intrathecal therapy[f,h]		
Leucovorin (generic)	50 mg/5 mL 500 mg/50 mL Vial	Solution for injection, intramuscular injection or intravenous use	$68.9400[b] $689.0000[b]	Block 2, Block 3 Days 10, 11: 15 mg/m^2/dose every 6 hours IV or orally	Block 2, Block 3 $68.94	Block 2, Block 3 $138
	5 mg	Tablet	$3.6776		Block 2, Block 3 $18.39	Block 2, Block 3 $37
Methotrexate (generic)	20 mg/2 mL 50 mg/2 mL Vial	Solution for intramuscular, intravenous, intraarterial, intrathecal, intracerebroventricular use	$12.5000 $8.9200	Block 2 Day 8: 1,000 mg/m^2/dose IV over 36 hrs For CNS 1, CNS 2 patients Day 8: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate[f] For CNS 3 and isolated CNS relapse patients Days 8, 22: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate as	Block 2 $249.76 For CNS 1, CNS 2 patients $8.92 For CNS 3 and isolated CNS relapse patients $8.92 Block 3 $129.34 For CNS 1, CNS 2, CNS 3 and isolated CNS relapse patients	Block 2 $250 For CNS 1, CNS 2 patients $9 For CNS 3 and isolated CNS relapse patients $18 Block 3 $259 For CNS 1, CNS 2, CNS 3 and isolated CNS relapse patients

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
				part of triple intrathecal therapy[f]	$8.92	$9
				Block 3 Day 1: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate[f] Day 8: 1,000 mg/m^2/dose IV over 36 hrs For CNS 1, CNS 2 patients Days 22: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate[f] For CNS 3 and isolated CNS relapse patients Day 22: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate as part of triple intrathecal therapy[f]	Cycle 1, Cycle 2 $8.92	Cycle 1, Cycle 2 $18
				Cycle 1 For CNS 1, CNS 2 patients Days 17, 29: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate[f,g] For CNS 3 and isolated CNS relapse patients Days 17, 29: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate as part of triple intrathecal therapy[f,g]		
				Cycle 2		

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
				For CNS 1, CNS 2 patients Days 9, 29: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate[f,h] For CNS 3 and isolated CNS relapse patients Day 9, 29: age-based dosing (8 mg to 15 mg) of intrathecal methotrexate as part of triple intrathecal therapy[f,h]		
Pegaspargase (Oncaspar)	3,750 U / 5 mL Vial	Solution for injection or infusion use	$6,115.9700[b,l]	Block 2 Days 9 or 10: 2,500 IU/m²/dose IV	Block 2 $6,115.97	Block 2 $6,116
Vincristine (generic)	1mg/mL Vial	Solution for infusion	$30.6000	Block 2, Bock 3 Day 1: 1.5 mg/m²/dose (max 2 mg) IV	Block 2, Block 3 $91.80	Block 2, Block 3 $92
Block 2 (4 weeks) Day 1-5: 3 mg/m²/dose twice daily of dexamethasone Day 1: 1.5 mg/m²/dose (max 2 mg) of vincristine Day 8: 1,000 mg/m²/dose IV methotrexate Day 10-11: 15 mg/m²/dose of leucovorin Day 9 or 10: 2,500 IU/m²/dose of pegaspargase Day 15-19: 440 mg/m²/dose of cyclophosphamide Day 15-19: 100 mg/m²/dose of etoposide For CNS 1, CNS 2 patients Day 8: age-based intrathecal methotrexate For CNS 3 and isolated CNS relapse patients Days 8, 22: age-based triple intrathecal therapy (cytarabine, hydrocortisone, methotrexate) therapy					$297.50 For CNS 1, CNS 2 patients $297.82 For CNS 3 and isolated CNS relapse patients $304.02	$8,330 For CNS 1, CNS 2 patients $8,339 For CNS 3 and isolated CNS relapse patients $8,513
Block 3 (4 weeks) Day 1-5: 3 mg/m²/dose twice daily of dexamethasone Day 1: 1.5 mg/m²/dose (max 2 mg) of vincristine Day 1,2,8, 9: 1,000 mg/m²/dose of cytarabine Day 1: age-based intrathecal methotrexate Day 2, 4, 9, 11, 23: 25,000 IU/m²/dose of erwinia asparaginase Day 8: 1,000 mg/m²/dose of IV methotrexate Day 10, 11: 15 mg/m²/dose of leucovorin For CNS 1, CNS 2 patients Day 22: age-based intrathecal methotrexate For CNS 3 patients Days 22: age-based triple intrathecal therapy (cytarabine, hydrocortisone, methotrexate)					$826.98 For CNS 1, CNS 2 patients $827.29 For CNS 3 and isolated CNS relapse patients $830.23	$23,155 For CNS 1, CNS 2 patients $23,164 For CNS 3 and isolated CNS relapse patients $23,247

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost[a]	Average treatment course cost
Block 2 and Block 3 chemotherapy						$31,485

CNS = central nervous system, IV = intravenous infusion

Note: Unit prices of medications are taken from the Ontario Drug Benefit Formulary (accessed September 26, 2024),[6] unless otherwise indicated, and do not include dispensing fees. For treatments using weight- or body surface area (BSA) based dosing, CADTH assumed a weight of 45 kg and 1.4m^2. All costs include wastage of unused medication in vials and do not include dispensing fees. Dosing is obtained from Brown et al. 2021,[3] and validated with clinical expert feedback.

[a] The average daily cost of each drug was calculated by dividing the treatment cost by the number of days over which the drug is administered. The average daily cost of each cycle or block was determined by dividing the total cycle or block cost by the duration of the cycle or block.

[b] IQVIA Delta PA database,[5] accessed September 9, 2024.

[c] According to the product monograph, blinatumomab IV bag can be changed every 24 hours, 48 hours, 72 hours, 96 hours or 7 days.[9] Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. Supervision by a healthcare professional or hospitalization is recommended for all subsequent cycle starts and reinitiations. Premedication is also recommended with 5 mg/m^2 of dexamethasone, to a maximum dose of 20 mg prior to the first dose of blinatumomab in the first cycle, prior to a step dose (such as Cycle 1 Day 8), or when restarting an infusion after an interruption of 4 or more hours in the first cycle. Intrathecal chemotherapy CNS prophylaxis is recommended before and during blinatumomab therapy to prevent central nervous system ALL relapse.

[d] The maximum dose of blinatumomab and step dosing for patients with M2 and M3 marrow was informed by clinical expert input.

[e] Expired price is not used in calculation of treatment costs.

[f] Age-based dosing was informed by clinical expert input.

[g] According to clinical expert feedback, intrathecal therapy may be administered at day 17 and 29 in clinical practice. In the study by Brown et al. 2021,[3] intrathecal therapy may be administered at day 15 and 29.

[h] According to clinical expert feedback, intrathecal therapy may be administered at day 9 and 29 in clinical practice. In the study by Brown et al. 2021,[3] intrathecal therapy may be administered at day 8 and 29.

[i] CADTH review of Rylaze.[8]

[j] At the time of this review, Erwinase was only available in Canada through exceptional importation and sale (i.e., it is a designated drug). CADTH was unable to independently verify the list price of Erwinase, nor the costs paid by jurisdictional drug plans through exceptional importation.[8] According to clinical experts input, Erwinase supply may be discontinued and replaced with Rylaze but the timeline for this change to take effect is uncertain.

[k] British Columbia pharmacare formulary, accessed September 9, 2024.

[l] This price was listed with an end date of December 16, 2019. The current wholesale price of pegaspargase is unknown.

References

1. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol*. 2016;75:40-46.
2. 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.
3. 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.
4. 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;41(25):4118-4129.
5. DeltaPA. Ottawa (ON): IQVIA; 2023: https://www.iqvia.com/. Accessed 2024 Oct 3.
6. Ontario Ministry of Health, Ontario Ministry of Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2024; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2024 Oct 3.
7. B.C. Government. BC PharmaCare formulary search. 2024; https://pharmacareformularysearch.gov.bc.ca. Accessed 2024 Oct 3.
8. CADTH Drug Reimbursement Review pharmacoeconomic report: Crisantaspase recombinant (Rylaze). *Can J Health Technol.* 2023;3(7). https://www.cda-amc.ca/sites/default/files/DRR/2023/PC0301-Rylaze.pdf. Accessed 2024 Oct 3.
9. Blincyto (blinatumomab): lyophilized powder for injection, 38.5mcg [product monograph]. Mississauga (ON): Amgen Canada Inc; 2024 Sep 28.