Blincyto® (blinatumomab)
(Intravenous)

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I. Length of Authorization

- Relapsed or Refractory B-Cell Precursor Acute Lymphocytic Leukemia (ALL)
  - Initial coverage will be provided for 30 weeks for a total of five cycles (2 cycles of induction followed by 3 cycles of consolidation)
  - Continued coverage will be provided every 24 weeks for a maximum of two additional authorizations (4 cycles of continued therapy)
- MRD+ B-Cell Precursor Acute Lymphocytic Leukemia (ALL)
  - Initial coverage will be provided for 24 weeks for a total of four cycles (1 cycle of induction followed by 3 cycles of consolidation)
  - Continued coverage may not be renewed

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Blincyto 35 mcg powder for injection: 28 vials per 42 day supply

B. Max Units (per dose and over time) [HCPCS Unit]:

- Relapsed or Refractory B-Cell Precursor Acute Lymphocytic Leukemia (ALL)
  Cycle 1 – 5 (Induction/Consolidation)
  - 980 billable units per 42 days
  Cycle 6 – 9 (Continued Therapy)
  - 980 billable units per 84 days
- MRD+ B-Cell Precursor Acute Lymphocytic Leukemia (ALL)
  Cycle 1 – 4 (Induction/Consolidation)
  - 980 billable units per 42 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 1 month old; **AND**

Universal Criteria [1]

- Used as single agent therapy; **AND**
- Patient has not received a live vaccine within 2 weeks prior to initiating therapy and will not receive concurrent treatment with lives vaccine while on therapy; **AND**

B-Cell Precursor Acute Lymphocytic Leukemia (ALL) † Φ [1-8,6e,7e]

- Patient has relapsed or refractory disease (Philadelphia chromosome [Ph]-positive patients must be TKI intolerant/refractory); **OR**
- Used as consolidation therapy in patients with minimal residual disease positive (MRD+) following a complete response/remission to induction therapy; **AND**
  - Patient has MRD (presence of leukemic cells) greater than or equal to 0.1% as measured by flow cytometry or polymerase chain reaction (PCR); **OR**
- Used in patients with MRD+ after consolidation therapy ‡

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA Approved Indication(s); ‡ Compendium Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria [1,2]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: Cytokine Release Syndrome (CRS), neurological toxicities, serious infections, pancreatitis, tumor lysis syndrome, neutropenia/febrile neutropenia, elevated liver enzyme, leukoencephalopathy, etc.; **AND**
- Treatment response or stabilization of disease as indicated by CBC, bone marrow cytogenic analysis, QPCR, or FISH; **AND**
  - Patient has not exceeded 4 cycles of continued therapy or 9 total cycles of therapy for the treatment of relapsed or refractory disease; **OR**
  - Continued therapy for use in the treatment of MRD+ ALL may not be renewed.

V. Dosage/Administration [1]

Indication	Dose
Acute Lymphoblastic Leukemia	**Relapsed/Refractory Disease*** ➢ Weight greater than or equal to 45 kg – Cycle 1 (induction): • 9 mcg daily x 7 days, then 28 mcg daily x 21 days in a 42 day cycle – Cycles 2-5 (induction/consolidation): • 28 mcg daily x 28 days in a 42 day cycle. – Cycles 6-9 (continued therapy): • 28 mcg daily x 28 days in an 84 day cycle. ➢ Weight less than 45 kg – Cycle 1(induction) : • 5 mcg/m2/day (not to exceed 9 mcg/day) x 7 days, then 15 mcg/m2/day (not to exceed 28 mcg/day) x 21 days in a 42 day cycle – Cycles 2-5 (induction/consolidation): • 15 mcg/m2/day (not to exceed 28 mcg/day) x 28 days in a 42 day cycle. – Cycles 6-9 (continued therapy): • 15 mcg/m2/day (not to exceed 28 mcg/day) x 28 days in an 84 day cycle. **Up to 9 total cycles of therapy.*
	MRD+ Disease* ➢ Weight greater than or equal to 45 kg – Cycle 1(induction): • 28 mcg daily x 28 days in a 42-day cycle – Cycles 2-4 (consolidation): • 28 mcg daily x 28 days in a 42 day cycle. ➢ Weight less than 45 kg – Cycle 1(induction) : • 15 mcg/m2/day (not to exceed 28 mcg/day) x 28 days in a 42 day cycle. – Cycles 2-4 (consolidation): • 15 mcg/m2/day (not to exceed 28 mcg/day) x 28 days in a 42 day cycle. **Up to 4 total cycles of therapy.*

VI. Billing Code/Availability Information

HCPCS Code:

- J9039 - Injection, blinatumomab, 1 microgram; 1 billable unit = 1 microgram

NDC:

- Blincyto 35 mcg single-use powder for injection: 55513-0160-xx

VII. References (STANDARD)

1. Blincyto [package insert]. Thousand Oaks, CA; Amgen, March 2021. Accessed March 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) blinatumomab. National Comprehensive Cancer Network, 2021. The

NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2021.

3. Jen EY, Xu Q, Schetter A, Przepiorka D, et al. FDA Approval: Blinatumomab for Patients with B-cell Precursor Acute Lymphoblastic Leukemia in Morphologic Remission with Minimal Residual Disease. Clin Cancer Res. 2019 Jan 15;25(2):473-477. doi: 10.1158/1078-0432.CCR-18-2337. Epub 2018 Sep 25.
4. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med 2017; 376:836-847. doi: 10.1056/NEJMoa1609783.
5. Martinelli G, Boissel N, Chevallier P, et al. Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study. J Clin Oncol. 2017 Jun 1;35(16):1795-1802. doi: 10.1200/JCO.2016.69.3531. Epub 2017 Mar 29.
6. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Pediatric Acute Lymphoblastic Leukemia 2.2021. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2021.
7. Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol. 2015;16(1):57-66.
8. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. J Clin Oncol. 2016;34(36):4381-4389. doi:10.1200/JCO.2016.67.3301.

VIII. References (ENHANCED)

1e. Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood. 2018 Apr 5;131(14):1522-1531. doi: 10.1182/blood-2017-08-798322. Epub 2018 Jan 22.

2e. Kantarjian H, DeAngelo D, Stelljes M, et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. N Engl J Med 2016; 375:740-753. DOI: 10.1056/NEJMoa1509277.

3e. Maude S, Laetsch T, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 2018; 378:439-448. DOI: 10.1056/NEJMoa1709866.

4e. Jeha S, Gaynon P, Razzouk, B, et al. Phase II Study of Clofarabine in Pediatric Patients With Refractory or Relapsed Acute Lymphoblastic Leukemia. Journal of Clinical Oncology 2006 24:12, 1917-1923.

5e. Benjamini O, Dumlao TL, Kantarjian H, et al. Phase II trial of hyper CVAD and dasatinib in patients with relapsed Philadelphia chromosome positive acute lymphoblastic leukemia or blast phase chronic myeloid leukemia. Am J Hematol. 2014 Mar;89(3):282-7.

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7e. Brown PA, Ji L, Xu X, et al. A Randomized Phase 3 Trial of Blinatumomab Vs. Chemotherapy As Post-Reinduction Therapy in High and Intermediate Risk (HR/IR) First Relapse of B-Acute Lymphoblastic Leukemia (B-ALL) in Children and Adolescents/Young Adults (AYAs) Demonstrates Superior Efficacy and Tolerability of Blinatumomab: A Report from Children's Oncology Group Study AALL1331. Blood 2019; 134 (Supplement_2): LBA–1. doi: https://doi.org/10.1182/blood-2019-132435.

8e. Topp MS, Kufer P, Gökbuget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol. 2011;29(18):2493-2498. doi:10.1200/JCO.2010.32.7270.

9e. Magellan Health, Magellan Rx Management. Blincyto Clinical Literature Review Analysis. Last updated March 2021. Accessed March 2021.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C83.50	Lymphoblastic (diffuse) lymphoma unspecified site
C83.51	Lymphoblastic (diffuse) lymphoma lymph nodes of head, face, and neck
C83.52	Lymphoblastic (diffuse) lymphoma intrathoracic lymph nodes
C83.53	Lymphoblastic (diffuse) lymphoma intra-abdominal lymph nodes
C83.54	Lymphoblastic (diffuse) lymphoma lymph nodes of axilla and upper limb
C83.55	Lymphoblastic (diffuse) lymphoma lymph nodes of inguinal region and lower limb
C83.56	Lymphoblastic (diffuse) lymphoma intrapelvic lymph nodes
C83.57	Lymphoblastic (diffuse) lymphoma spleen
C83.58	Lymphoblastic (diffuse) lymphoma lymph nodes of multiple sites
C83.59	Lymphoblastic (diffuse) lymphoma extranodal and solid organ sites
C91.00	Acute lymphoblastic leukemia not having achieved remission

C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdictio	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT,	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; CRh = complete response with partial hematologic recovery; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; RFS = relapse-free survival; Ph = Philadelphia chromosome; TKI = tyrosine kinase inhibitor; SOC = standard of care; AE = adverse event

B-Cell Precursor Acute Lymphoblastic Leukemia (ALL) †

Ph-negative Relapsed or Refractory ALL							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Blinatumomab	1 preferred for relapsed/ refractory Philadelphia-chromosome negative B-ALL	Yes (Not restrictive of Ph-status)	Phase 3 (TOWER), randomized	Standard of care: • FLAG ± anthracycline-based regimen • HiDAC-based regimen • High-dose methotrexate-based regimen • Clofarabine-based regimen	OS	Relapsed or refractory disease	• Treatment with blinatumomab resulted in significantly longer OS than chemotherapy
Inotuzumab ozogamicin	1 preferred for relapsed/ refractory Philadelphia-chromosome negative B-ALL	Yes (Not restrictive of Ph-status)	Phase 3 (INO-VATE), randomized, open-label	Standard of care: • FLAG • HiDAC-based regimen	CR and OS	Relapsed or refractory CD22-positive Ph+ or Ph-negative ALL in patients due for first or second salvage treatment. Ph+ patients were required to have failed treatment	• Patients receiving inotuzumab ozogamicin versus standard care achieved higher response, MRD-negativity rates, and prolonged PFS and OS

						with at least 1 TKI and standard chemotherapy	
Tisagenlecleucel	2A preferred for relapsed/ refractory Philadelphia-chromosome negative B-ALL in patients < 26 years and with refractory disease or ≥ 2 relapses	Yes for patients up to 25 years of age with B-cell ALL that is refractory or in second or later relapse (Not restrictive of Ph-status)	Phase 2 (ELIANA), single-cohort	N/A	ORR	Relapsed or refractory disease Excluded patients with previous anti-CD19 therapy	• Tisagenlecleucel provided durable remission with long-term persistence in pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects
Other chemotherapy	2A						
Ph-positive Relapsed or Refractory ALL							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Blinatumomab	2A for relapsed/ refractory Philadelphia chromosome-positive TKI intolerant/ refractory B-ALL	Yes (Not restrictive of Ph-status)	Phase 2 (ALCANTARA), open-label, single-arm	N/A	CR or CRh	After imatinib and at least one second-generation or later TKI	• Blinatumomab demonstrated antileukemia activity in high-risk patients with Ph+ ALL who had relapsed or were refractory to TKIs
Inotuzumab ozogamicin	2A for relapsed/ refractory Philadelphia chromosome-positive TKI	Yes (Not restrictive of Ph-status)	Phase 3 (INO-VATE), randomized, open-label	SOC • FLAG • HiDAC-based regimen	CR and OS	Relapsed or refractory CD22-positive Ph+ or Ph-negative ALL in patients due for first or second salvage treatment.	• Patients receiving inotuzumab ozogamicin versus standard care achieved higher response, MRD-

	intolerant/ refractory B-ALL					Ph+ patients were required to have failed treatment with at least 1 TKI and standard chemotherapy	negativity rates, and prolonged PFS and OS • However, CR was not statistically significantly higher in patients with Ph+ disease
Tisagenlecleucel	2A for relapsed/ refractory Philadelphia-chromosome positive B-ALL in patients < 26 years and with refractory disease or ≥ 2 relapses	Yes for patients up to 25 years of age with B-cell ALL that is refractory or in second or later relapse (Not restrictive of Ph-status)	Phase 2 (ELIANA), single-cohort	N/A	ORR	Relapsed or refractory disease	• Tisagenlecleucel provided durable remission with long-term persistence in pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects
Clofarabine	2A	Yes (age 1-21 years old)	Phase 2, open-label	N/A	Overall remission rate	Relapsed or refractory disease	• Clofarabine is active as a single agent in pediatric patients with multiple relapsed or refractory ALL.
Hyper-CVAD+ dasatinib (if not used for induction)	2A	Yes	Phase 2	N/A		Relapsed disease	• HyperCVAD regimen with dasatinib is effective in patients with relapsed Ph-positive ALL and CML
Other generic regimens	2A						
Minimal Residual Disease positive (MRD+)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Blinatumomab	2A for Ph-negative disease (No recom-mendation for Ph+)	Yes for first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% (Not restrictive of Ph-status)	Phase 2 (BLAST), single-arm, open-label	N/A	Rate of complete MRD response after 1 cycle of blinatumo mab	Patients in first or later CR with persistent or recurrent MRD ($\geq 10^{-3}$) after at least 3 intensive chemotherapy treatments	• Blinatumomab treatment resulted in a complete MRD response rate of 78%
Blinatumomab	2A for Ph-negative disease (No recom-mendation for Ph+)	Yes for first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% (Not restrictive of Ph-status)	Phase 2	N/A	-----	Patients with MRD persistence or relapse after induction and consolidation therapy	• Blinatumomab is an efficacious and well-tolerated treatment in patients with MRD-positive B-lineage ALL after intensive chemotherapy. 16 out of 21 patients became MRD negative.

Pediatric Acute Lymphoblastic Leukemia

Consolidation therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Blinatumomab	2A	No	Phase 3 (COGS AALL1331), randomized	Chemotherapy (UKALLR3)	DFS	Following 1 cycle of re-induction chemotherapy (post-reinduction	• For children and adolescents/young adults with high risk or intermediate risk first relapse of B-ALL

						consolidation therapy)	blinatumomab is superior to standard therapy as post-reinduction consolidation prior to HSCT, resulting in fewer and less severe toxicities, higher rates of MRD response, greater likelihood of proceeding to HSCT and improved disease-free and overall survival.
Philadelphia Chromosome positive or negative – Relapsed or Refractory							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Blinatumomab	2A	Yes	Phase 1/2, open-label	N/A	Complete remission	Relapsed or refractory disease	• Blinatumomab demonstrated antileukemic activity with complete minimal residual disease response (52% of patients with complete remission within first 2 cycles) in children with relapsed/refractory BCP-ALL.