Mylotarg™ (gemtuzumab ozogamicin)
(Intravenous)

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I. Length of Authorization [1,5-8,11]

Newly-Diagnosed AML

- In combination with daunorubicin and cytarabine (adult): Coverage will be provided for 6 months consisting of 3 cycles (1 induction and 2 consolidation) and may NOT be renewed.
- In combination with daunorubicin and cytarabine (pediatric): Coverage will be provided for 6 months consisting of 2 cycles (1 induction and 1 consolidation) and may NOT be renewed.
- In combination with idarubicin and cytarabine (adult): Coverage will be provided for 6 months consisting of 3 cycles (1 induction and 2 consolidation) and may NOT be renewed.
- In combination with high-dose cytarabine (adult) as consolidation therapy: Coverage will be provided for 6 months consisting of 2 cycles (2 doses) and may NOT be renewed.
- Single-agent therapy: Coverage will be provided for 6 months and may be renewed. Coverage is provided for 1 cycle of induction and up to a maximum of 8 cycles of continuation.

Relapsed or Refractory AML

- Coverage will be provided for 6 months consisting of 1 cycle (3 doses) and may NOT be renewed.

Acute Promyelocytic Leukemia (APL)

- Induction/Consolidation Therapy: Coverage will be provided for 6 months and may be renewed. Coverage is provided for 1 cycle of induction therapy followed by consolidation therapy. *[Note: Duration of consolidation therapy is dependent on disease risk severity (see below)]*
    - High-risk disease: Coverage will be provided until molecular complete response.
- Therapy for first relapse:
    - Single-agent therapy: Coverage will be provided for 6 total doses
    - Use in combination with arsenic trioxide: Coverage will be provided for 6 months and may be renewed until bone marrow confirmation of remission.
- Therapy for leukocytosis associated with differentiation syndrome:
    - Coverage will be provided for one cycle (up to 3 total doses) and may NOT be renewed.

II. Dosing Limits

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

- AML:
  - Induction: 135 billable units on Day 1, 90 billable units on Day 4, 90 billable units on Day 7 of a 28-day cycle (1 cycle only)
  - Consolidation/Continuation: 225 billable units every 28 days
- APL:
  - Induction: 180 billable units on Day 1
  - Consolidation/Relapse: 270 billable units every 28 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age (unless otherwise specified); **AND**
- Patient has not previously received gemtuzumab ozogamicin; **AND**
- Baseline electrocardiogram (ECG) has been obtained in patients with a history of or predisposition for QTc prolongation; **AND**

Universal Criteria [1]

- Patient has CD33-positive disease; **AND**

Acute Myeloid Leukemia (AML) † ‡ Φ [1,6,10]

- Patient has newly-diagnosed disease; **AND**
  - Used in combination with daunorubicin and cytarabine †; **AND**
    - Patient is at least 1 month of age; **OR**
  - Used as a single agent †; **OR**
  - Used in combination with cytarabine and idarubicin; **AND**
    - Used as induction or consolidation therapy; **AND**
    - Patient has favorable or intermediate-risk AML; **OR**
  - Used in combination with high-dose cytarabine; **AND**
    - Used as consolidation therapy; **AND**
    - Patient has favorable-risk AML; **OR**
- Patient has relapsed or refractory disease; **AND**
  - Used as a single agent †; **AND**
  - Patient is at least 2 years of age; **OR**
- Patient has acute promyelocytic leukemia (APL); **AND**
  - Used for high-risk disease (white blood cell count >10 x 10^9/L); **AND**
    - Used as induction therapy; **AND**

- Used in combination with tretinoin (ATRA) and arsenic trioxide (ATO); **OR**
- Used in combination with ATRA in patients with prolonged QTc **Ω**; **OR**

▪ Used as consolidation therapy; **AND**

- Used in combination with tretinoin (ATRA) or arsenic trioxide (ATO); **OR**

○ Used for first relapse **Ω** (morphologic or molecular); **AND**

▪ Used as a single agent; **AND**

- Used for early relapse (<6 months) after tretinoin (ATRA) and arsenic trioxide (ATO); **OR**

▪ Used in combination with ATO (with or without ATRA); **AND**

- Patient has no prior exposure to ATO; **OR**
- Used for early relapse (<6 months) after an ATRA + anthracycline-containing regimen; **OR**
- Used for late relapse (≥ 6 months) after an ATO containing regimen; **OR**

○ Used for leukocytosis associated with differentiation syndrome **Ω**; **AND**

▪ Used as a single agent for difficult-to-treat cases

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.

Ω *Please note that the supporting data for this indication has been assessed and deemed to be of insufficient quality based on the review conducted for the Enhanced Oncology Value (EOV) program. However, due to the absence of viable alternative treatment options, this indication will be retained in our policy and evaluated on a case-by-case basis.*

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

IV. Renewal Criteria [1,6]

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the universal and indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Duration of authorization has not been exceeded *(refer to Section I)*; **AND**
- Disease stabilization or improvement as evidenced by a complete response [CR] (i.e. morphologic, cytogenetic or molecular complete response CR), complete hematologic response or a partial response by CBC, bone marrow cytogenic analysis, QPCR, or FISH; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe infusion-related reactions (including anaphylaxis), hemorrhage, hepatotoxicity (e.g.,

veno-occlusive liver disease [VOD], sinusoidal obstruction syndrome [SOS], etc.), QTc interval prolongation, etc.

V. Dosage/Administration [1,5-8,11,13,14]

Indication	Dose

Acute Myeloid Leukemia	**Newly Diagnosed AML**
	<u>Adult (≥ 18 years old) – Combination regimen:</u>
	• Induction Therapy (1 cycle only):
	  ○ Administer 3 mg/m^2 (up to one 4.5 mg vial) on Days 1, 4, and 7 in combination with daunorubicin and cytarabine
	  ○ For patients requiring a second induction cycle, do not administer gemtuzumab ozogamicin during the second induction cycle
	• Consolidation Therapy (maximum of 2 cycles):
	  ○ Administer 3 mg/m^2 (up to one 4.5 mg vial) on Day 1 in combination with daunorubicin or idarubicin and cytarabine
	  ○ Administer 3 mg/m^2 (up to one 4.5 mg vial) on Day 1 in combination with high-dose cytarabine
	<u>Pediatric (1 month to < 18 years old) – Combination regimen:</u>
	• Induction Therapy (1 cycle only):
	  ○ Administer 3 mg/m^2 (BSA ≥ 0.6 m^2) or 0.1 mg/kg (BSA < 0.6 m^2) on Day 6 in combination with daunorubicin and cytarabine
	  ○ For patients requiring a second induction cycle, do not administer gemtuzumab ozogamicin during the second induction cycle
	• Consolidation/Intensification Therapy (1 cycle only):
	  ○ Administer 3 mg/m^2 (BSA ≥ 0.6 m^2) or 0.1 mg/kg (BSA < 0.6 m^2) on Day 7 in intensification 2
	<u>Adult (≥ 18 years old) – Single-agent regimen:</u>
	• Induction Therapy (1 cycle only):
	  ○ Administer 6 mg/m^2 as a single agent on Day 1 and 3 mg/m^2 on Day 8
	• Continuation Therapy:
	  ○ Administer 2 mg/m^2 as a single agent on Day 1 every 4 weeks (maximum of 8 cycles); OR
	  ○ Administer 6 mg/m^2 as a single agent on Day 1 and 3 mg/m^2 on Day 8

	Relapsed or Refractory AML • Administer 3 mg/m^2 (up to one 4.5 mg vial) on Days 1, 4, and 7 (1 cycle only)

	Acute Promyelocytic Leukemia (APL)
	<u>High-Risk Disease:</u>
	• Induction Therapy (1 cycle only):
	  ○ Administer 6-9 mg/m^2 on Day 1 (or Day 2, Day 3, or Day 4) in combination with ATRA with or without ATO
	• Consolidation Therapy:
	  ○ ATRA and ATO are used for consolidation. If ATRA or ATO are discontinued due to toxicity, a single dose of gemtuzumab ozogamicin 9 mg/m2 may be

	given once every 4-5 weeks provided platelets and ANC recover to ≥100 and ≥1.0, respectively, until molecular complete remission.
	
	Therapy for First Relapse:
	• Single-agent:
	  ○ Administer 6 mg/m^2 on Day 1 and Day 15 (up to a maximum of 6 total doses)
	• In combination with ATO (with or without ATRA):
	  ○ Administer 9 mg/m^2 on Day 1 as a single dose until count recovery with marrow confirmation of remission.
	Therapy for of leukocytosis associated with differentiation syndrome:
	• Administer 3 mg/m^2 (up to one 4.5 mg vial) on Days 1, 4, and 7 (1 cycle only)

VI. Billing Code/Availability Information

HCPCS Code:

- J9203 – Injection, gemtuzumab ozogamicin, 0.1 mg: 1 billable unit = 0.1 mg

NDC:

- Mylotarg 4.5 mg single-dose vial: 00008-4510-xx

VII. References (STANDARD)

1. Mylotarg [package insert]. Philadelphia, PA; Pfizer Inc., August 2021. Accessed March 2025.
2. Castaigne S, Pautas C, Terré C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet. 2012 Apr 21;379(9825):1508-16
3. Amadori S, Suciu S, Selleslag D, et al. Gemtuzumab Ozogamicin Versus Best Supportive Care in Older Patients With Newly Diagnosed Acute Myeloid Leukemia Unsuitable for Intensive Chemotherapy: Results of the Randomized Phase III EORTC-GIMEMA AML-19 Trial. J Clin Oncol. 2016 Mar 20;34(9):972-9.
4. Taksin AL, Legrand O, Raffoux E, et al. High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: A prospective study of the ALFA group. Leukemia 2007;21:66–71.
5. Abaza Y, Kantarjian H, Garcia-Mannero G, et al. Long-term outcome of acute promyelocytic leukemia treated with all-transretinoic acid, arsenic trioxide, and gemtuzumab. Blood 2017;129:1275-1283.
6. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Acute Myeloid Leukemia. Version 2.2025. National Comprehensive Cancer Network, 2025. 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 2025.

7. Burnett AK, Hills RK, Milligan D, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. J Clin Oncol. 2011 Feb 1;29(4):369-77. doi: 10.1200/JCO.2010.31.4310.
8. Hills RK, Castaigne S, Appelbaum FR, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. Lancet Oncol. 2014;15(9):986–996. doi:10.1016/S1470-2045(14)70281-5.
9. Gamis AS, Alonzo TA, Meshinchi S, et al. Gemtuzumab ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Children's Oncology Group trial AAML0531. J Clin Oncol. 2014;32(27):3021-3032. doi:10.1200/JCO.2014.55.3628.
10. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) gemtuzumab ozogamicin. National Comprehensive Cancer Network, 2025. 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 2025.
11. Estey EH, Giles FJ, Beran M, et al. Experience with gemtuzumab ozogamycin ("mylotarg") and all-trans retinoic acid in untreated acute promyelocytic leukemia. Blood. 2002 Jun 1;99(11):4222-4. doi: 10.1182/blood-2001-12-0174. PMID: 12010830.
12. Lo-Coco F, Cimino G, Breccia M, et al. Gemtuzumab ozogamicin (Mylotarg) as a single agent for molecularly relapsed acute promyelocytic leukemia. Blood. 2004 Oct 1;104(7):1995-9.
13. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gemtuzumab ozogamicin: Acute Myeloid Leukemia Chemotherapy Order Template, AML88. National Comprehensive Cancer Network, 2025. 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 Guidelines, go online to NCCN.org. Accessed March 2025.
14. Larson R. (2024) Acute myeloid leukemia: Induction therapy in medically fit adults. UptoDate. Last updated: Dec 13, 2023. Accessed: March 2025. Available from https://www.uptodate.com/contents/acute-myeloid-leukemia-induction-therapy-in-medically-fit-adults?sectionName=Gemtuzumab%20ozogamicin&search=gemtuzumab%20leukocytosis&topicRef=4522&anchor=H3717141861&source=see_link#H3717141861.

VIII. References (ENHANCED)

1e. Burnett AK, Russell NH, Hills RK, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. J Clin Oncol. 2012 Nov 10;30(32):3924-31. doi: 10.1200/JCO.2012.42.2964. J Clin Oncol. 2013 Dec 10;31(35):4424-30. doi: 10.1200/JCO.2013.49.0771.

2e. Amadori S, Suciu S, Stasi R, et al. Sequential combination of gemtuzumab ozogamicin and standard chemotherapy in older patients with newly diagnosed acute myeloid leukemia: results of a randomized phase III trial by the EORTC and GIMEMA consortium (AML-17).

3e. Ravandi F, Estey E, Jones D, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. J Clin Oncol. 2009;27(4):504–510. doi:10.1200/JCO.2008.18.6130.

4e. Burnett AK, Russell NH, Hills RK, et al. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2015 Oct;16(13):1295-305. doi: 10.1016/S1470-2045(15)00193-X.

5e. Lancet JE, Moseley A, Komrokji RS, et al. ATRA, Arsenic Trioxide (ATO), and Gemtuzumab Ozogamicin (GO) Is Safe and Highly Effective in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia (APL): Final Results of the SWOG/Alliance/ECOG S0535 Trial. Blood. 2016;128:896.

6e. Aribi A, Kantarjian HM, Estey EH, et al. Combination therapy with arsenic trioxide, all-trans retinoic acid, and gemtuzumab ozogamicin in recurrent acute promyelocytic leukemia. Cancer. 2007 Apr 1;109(7):1355-9.

7e. Burnett AK, Hills RK, Milligan D, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. J Clin Oncol. 2011 Feb 1;29(4):369-77.

8e. Jaramillo S, Benner A, Krauter J, et al. Condensed versus standard schedule of high-dose cytarabine consolidation therapy with pegfilgrastim growth factor support in acute myeloid leukemia. Blood Cancer J 2017;7:e564.

9e. Sanz MA, Montesinos P, Rayon C, et al. Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. Blood 2010;115:5137-5146.

10e. Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. J Clin Oncol. 2010 Feb 10;28(5):808-14. doi: 10.1200/JCO.2009.23.2652. Epub 2010 Jan 4. PMID: 20048183.

11e. Teuffel O, Leibundgut K, Lehrnbecher T, et al. Anthracyclines during induction therapy in acute myeloid leukaemia: a systematic review and meta-analysis. Br J Haematol. 2013 Apr;161(2):192-203. doi: 10.1111/bjh.12233. Epub 2013 Feb 8. PMID: 23398482.

12e. Prime Therapeutics Management. Mylotarg Clinical Literature Review Analysis. Last updated March 2025. Accessed March 2025.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C92.00	Acute myeloblastic leukemia not having achieved remission
C92.01	Acute myeloblastic leukemia in remission

C92.02	Acute myeloblastic leukemia in relapse
C92.40	Acute promyelocytic leukemia not having achieved remission
C92.41	Acute promyelocytic leukemia in remission
C92.42	Acute promyelocytic leukemia in relapse
C92.50	Acute myelomonocytic leukemia not having achieved remission
C92.51	Acute myelomonocytic leukemia in remission
C92.52	Acute myelomonocytic leukemia in relapse
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.61	Acute myeloid leukemia with 11q23-abnormality in remission
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.A0	Acute myeloid leukemia with multilineage dysplasia not having achieved remission
C92.A1	Acute myeloid leukemia with multilineage dysplasia in remission
C92.A2	Acute myeloid leukemia with multilineage dysplasia in relapse
C93.00	Acute monoblastic/monocytic leukemia not having achieved remission
C93.01	Acute monoblastic/monocytic leukemia in remission
C93.02	Acute monoblastic/monocytic leukemia in relapse

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

The preceding information is intended for non-Medicare coverage determinations. 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 Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied 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		
Jurisdiction	**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, AZ	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.

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
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