Mylotarg™ (gemtuzumab ozogamicin)
(Intravenous)

-E-

Document Number: EOCCO-0491

Last Review Date: 12/07/2023
Date of Origin: 09/03/2019
Dates Reviewed: 09/2019, 12/2019, 11/2020, 12/2021, 12/2022, 12/2023

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.
- 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 one 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 for consolidation therapy will be provided for 2 cycles.

II. Dosing Limits

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

- Mylotarg 4.5 mg single-dose vial: 7 vials per initial 28 days; 6 vials per 28 days thereafter

B. 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: 270 billable units every 28 days (2 cycles only)

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 †; **AND**
    - Patient is > 60 years of age; **OR**
- Patient is in first relapse or has refractory diseases; **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 as consolidation therapy; **AND**
      - Used following treatment with tretinoin (ATRA) and arsenic trioxide (ATO)

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 [1,6]

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**
- 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.; **AND**
    - Patients receiving single-agent treatment for newly-diagnosed AML have not exceeded the maximum of 8 cycles of continuation (adult only); **OR**
    - Patients receiving consolidation therapy for acute promyelocytic leukemia (APL):
        - High-risk disease: Therapy has not exceeded the maximum of 2 cycles

Note: treatment of newly diagnosed AML in combination with chemotherapy and relapsed or refractory AML may NOT be renewed.

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

Indication	Dose
Acute Myeloid Leukemia	**Newly Diagnosed AML**
	Adult (≥ 18 years old) – Combination regimen: • 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 and 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 + ATO
	• Consolidation Therapy:
	  ○ Administer 9 mg/m^2 for 2 cycles

VI. Billing Code/Availability Information

<u>HCPCS Code:</u>

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

<u>NDC:</u>

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

VII. References (STANDARD)

1. Mylotarg [package insert]. Philadelphia, PA; Pfizer Inc., August 2021. Accessed October 2023.

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 5.2023. National Comprehensive Cancer Network, 2023. 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 October 2023.
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, 2023. 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 October 2023.

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.

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. 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.
7e. 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.
8e. 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.
9e. Prime Therapeutics Management. Mylotarg Clinical Literature Review Analysis. Last updated October 2023. Accessed October 2023.

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
C92.50	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)

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: https://www.cms.gov/medicare-coverage-database/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		
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)

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
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