# Mylotarg™ (gemtuzumab ozogamicin)
## (Intravenous)

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Document Number: IC-0491

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## I. Length of Authorization

Newly-Diagnosed AML

- De novo disease 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.
- De novo disease 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 use: 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.

Post-Remission Therapy for AML

- Coverage will be provided for 6 months consisting of 2 cycles (2 doses) and may not be renewed.

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

- Induction/Consolidation 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 7 cycles of consolidation.

## II. Dosing Limits

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

- Mylotarg 4.5 mg vial: 5 vials per initial 28 days; 1 vial per 28 days thereafter

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

| | Induction (1 cycle only) | Consolidation |
|---|---|---|

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| **AML** | •135 billable units on Day 1 & 90 billable units on Day 8 of a 28-day cycle; **OR**<br>•45 billable units on Days 1, 4, & 7 of a 28-day cycle | •45 billable units on Day 1 of a 28-day cycle (up to a maximum of 8 subsequent cycles) |
| **APL** | 180 billable units on Day 1 | •180 billable units on Day 1 of a 28-day cycle |

## 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) 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]**

- Patient has newly-diagnosed disease; **AND**
  - Used in combination with daunorubicin and cytarabine; **AND**
    - Patient has de novo disease; **AND**
      - Patient is 1 month or older; **OR**
    - Patient has favorable or intermediate-risk cytogenetics; **OR**
  - Used as a single agent; **AND**
    - Patient is ≥ 60 years old or is not able to tolerate intensive therapy with daunorubicin and cytarabine; **OR**
- Used as post-remission therapy; **AND**
  - Used in combination with daunorubicin and intermediate-dose cytarabine; **AND**
    - Patient ≥ 60 years old and obtained a complete response to previous intensive therapy with gemtuzumab ozogamicin plus daunorubicin and cytarabine induction therapy; **OR**
    - Patient < 60 years old with core binding factor (CBF) cytogenetic translocations without KIT mutations or intermediate-risk cytogenetics and/or molecular abnormalities; **OR**
  - Used in combination with high-dose cytarabine; **AND**
    - Patient is less than 60 years old with core binding factor (CBF) cytogenetic translocations without KIT mutations; **OR**
- Used for patients in first relapse; **AND**
  - Used as a single agent †; **AND**
    - Patient is 2 years or older; **OR**
- Patient has acute promyelocytic leukemia ‡; **AND**

- Used as induction and consolidation therapy in patients with high risk disease (white blood cell count >10 X $10^9$/L); **AND**
  - Used in combination with tretinoin (ATRA) and/or 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 can be renewed based upon the following criteria:

- Patient continues to meet 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 the following: severe infusion-related reactions, hemorrhage, hepatotoxicity including hepatic veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS), 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) have not exceeded the maximum of 7 cycles of therapy

Note: treatment of newly diagnosed de novo AML, relapsed or refractory AML, and post-remission therapy for AML are not renewable.

## V. Dosage/Administration [1,7,8]

| Indication | Dose |
|---|---|
| Acute Myeloid Leukemia | **Newly Diagnosed AML** |
| | Adult (≥ 18 years old) – Combination regimen (De Novo AML):<br>• Induction Therapy (1 cycle only):<br>  ○ 3 mg/m² (up to one 4.5 mg vial) on Days 1, 4, and 7 in combination with daunorubicin and cytarabine<br>  ○ For patients requiring a second induction cycle, do not administer gemtuzumab ozogamicin during the second induction cycle |

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| | • Consolidation Therapy (maximum of 2 cycles):<br>  ○ 3 mg/m² (up to one 4.5 mg vial) on Day 1 in combination with daunorubicin and cytarabine<br><u>Pediatric (1 month to < 18 years old) – Combination regimen (De Novo AML):</u><br>• Induction Therapy (1 cycle only):<br>  ○ 3 mg/m² (BSA ≥ 0.6 m²) or 0.1 mg/kg (BSA < 0.6 m²) on Day 6 in combination with daunorubicin and cytarabine<br>  ○ For patients requiring a second induction cycle, do not administer gemtuzumab ozogamicin during the second induction cycle<br>• Consolidation/Intensification Therapy (1 cycle only):<br>  ○ 3 mg/m² (BSA ≥ 0.6 m²) or 0.1 mg/kg (BSA < 0.6 m²) on Day 7 in Intensification 2<br><u>Single-agent regimen:</u><br>• Induction Therapy (1 cycle only):<br>  ○ 6 mg/m² as a single agent on Day 1, and 3 mg/m² on Day 8<br>• Continuation Therapy (maximum of 8 cycles):<br>  ○ 2 mg/m² as a single agent on Day 1 every 4 weeks |
| | **Post-Remission Therapy for AML** |
| | <u>Combination regimen:</u><br>• 3 mg/m² (up to one 4.5 mg vial) on day 1 in combination with daunorubicin and cytarabine (2 cycles only)<br>• 3 mg/m² (up to one 4.5 mg vial) on day 1 in combination with high-dose cytarabine (2 cycles only) |
| | **Relapsed or Refractory AML (single agent)** |
| | • 3 mg/m² (up to one 4.5 mg vial) on Days 1, 4, and 7 (1 cycle only) |
| | **Acute Promyelocytic Leukemia** |
| | <u>Combination regimen:</u><br>• Induction Therapy (1 cycle only):<br>  ○ 6-9 mg/m² on Day 1 in combination with ATRA+ATO<br>• Consolidation Therapy (up to a maximum of 7 cycles):<br>  ○ ATRA and ATO are used for consolidation. If ATRA or ATO are discontinued due to toxicity then: Mylotarg, single agent, dosed at 9mg/m2 on Day 1 every 4-5 weeks until 28 weeks from complete remission |

## 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., June 2020. Accessed October 2020.

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.
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6. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Acute Myeloid Leukemia. Version 1.2021. National Comprehensive Cancer Network, 2020. 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 2020.
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.
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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. Palmetto GBA, LLC. Local Coverage Article (LCA): Billing and Coding: Chemotherapy (A56141). Centers for Medicare & Medicaid Services, Inc. Updated on 05/26/2020 with effective date 04/30/2020. Accessed October 2020.

## 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. Magellan Health, Magellan Rx Management. Mylotarg Clinical Literature Review Analysis. Last updated October 2020. Accessed October 2020.

## 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 |
| C94.00 | Acute erythroid leukemia not having achieved remission |
| C94.01 | Acute erythroid leukemia in remission |
| C94.02 | Acute erythroid leukemia in relapse |
| C94.20 | Acute megakaryoblastic leukemia not having achieved remission |
| C94.21 | Acute megakaryoblastic leukemia in remission |
| C94.22 | Acute megakaryoblastic 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):

| | |
|---|---|
| **Jurisdiction(s):** J & M | **NCD/LCD/LCA Document (s):** A56141 |
| https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=57249&ver=2&DocID=A56141&bc=gAAAABAAAAAA& | |

| 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. |
| 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; CRi = complete response with incomplete 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; QOL = quality of life

### Acute Myeloid Leukemia (AML)

| Newly-diagnosed disease – Induction/Consolidation (Post-remission therapy) | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Regimen** | **NCCN Category** | **FDA Approved** | **Trial Design** | **Comparator** | **Primary End-Point** | **Line of Therapy** | **Conclusion** |
| Gemtuzumab ozogamicin + daunorubicin + cytarabine | 2A (preferred for <60 years old with favorable risk) | Yes | Phase 3 (ALFA-0701), randomized, open-label | Daunorubicin + cytarabine (7+3) | EFS | Induction and consolidation therapy | • Gemtuzumab ozogamicin improved EFS compared to standard 7+3 therapy alone however, there was no significant difference in OS. |
| Gemtuzumab ozogamicin + daunorubicin + cytarabine | 2A (preferred for <60 years old with favorable risk) | Yes | Phase 3 (AML-16), randomized, multi-center | Daunorubicin + cytarabine (7+3) | OS | Induction therapy | • The addition of gemtuzumab ozogamicin to standard induction therapy reduced the risk of relapse however, there was no significant difference in OS. |
| Gemtuzumab ozogamicin + mitoxantrone + cytarabine + etoposide | None | No | Phase 3 (AML-17), randomized | Mitoxantrone + cytarabine + etoposide | OS | Induction and/or consolidation therapy | • The combination of GO and standard chemotherapy provides no benefit for older patients with AML and is too toxic for those age ≥ 70 years. |
| Gemtuzumab ozogamicin + standard therapy (daunorubicin + cytarabine; | 2A | Yes | AML-15, randomized, open-label | Standard induction or consolidation therapy | ORR<br>OS | Induction and/or consolidation therapy | • The addition of gemtuzumab ozogamicin to standard induction chemotherapy demonstrated a significant benefit in survival compared to standard chemotherapy alone in younger patients |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| cytarabine + daunorubicin, + etoposide; or fludarabine + cytarabine + granulocyte colony-stimulating factor + idarubicin) | | | | | | | with previously untreated AML with favorable-risk cytogenetics. |
| Gemtuzumab ozogamicin + induction chemotherapy | 2A | Yes | Meta-analysis of 5 randomized controlled trials | Chemotherapy alone | OS | Induction therapy | • Gemtuzumab ozogamicin can be safely added to conventional induction therapy and provides a significant survival benefit for patients without adverse cytogenetic characteristics |
| Gemtuzumab ozogamicin (GO) + daunorubicin + cytarabine + etoposide | 2A | Yes in patients ≥1 month old | Phase 3 (AAML0531), randomized | Daunorubicin + cytarabine + etoposide | EFS<br>OS | Newly diagnosed de novo AML | • Gemtuzumab ozogamicin added to chemotherapy improved EFS through a reduction in relapse risk for children and adolescents with newly diagnosed AML. There were no differences in overall survival between the 2 arms. |
| Gemtuzumab ozogamicin | 2A | Yes | Phase 3 (AML-19), randomized, multi-center, open-label | Best supportive care (BSC) | OS | Induction therapy and consolidation therapy | • First-line monotherapy with low-dose GO, as compared with BSC, significantly improved OS in older patients with acute myeloid leukemia who were ineligible for intensive chemotherapy. No unexpected AEs were identified and toxicity was manageable. |
| **Relapsed or refractory disease** | | | | | | | |
| **Regimen** | **NCCN Category** | **FDA Approved** | **Trial Design** | **Comparator** | **Primary End-Point** | **Line of Therapy** | **Conclusion** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gemtuzumab ozogamicin | 2A | Yes | Phase 2 (MyloFrance-1) | N/A | ----- | First relapse | • Gemtuzumab ozogamicin demonstrated a CR rate of 26% in AML patients in first relapse. |
| **Acute promyelocytic leukemia – induction therapy** | | | | | | | |
| **Regimen** | **NCCN Category** | **FDA Approved** | **Trial Design** | **Comparator** | **Primary End-Point** | **Line of Therapy** | **Conclusion** |
| Gemtuzumab ozogamicin (GO)+ tretinoin (ATRA) ± arsenic trioxide (ATO) | 2A preferred | No | Prospective trial | N/A | ----- | Induction and consolidation therapy | • The combination of ATRA and ATO (with or without GO) as initial therapy for APL was effective with a complete response rate of 92%. |
| Gemtuzumab ozogamicin + tretinoin (ATRA) ± arsenic trioxide (ATO) | 2A preferred | No | Long-term study | N/A | ----- | Newly diagnosed | • The combination of ATRA and ATO with GO elicits durable responses with an 86% overall survival at 5 years. |
| Gemtuzumab ozogamicin (high-risk) + tretinoin (ATRA) + arsenic trioxide (ATO) | 2A preferred | No | Phase 3 (AML17), randomized, controlled, multi-center | Gemtuzumab ozogamicin (high-risk) + tretinoin (ATRA) + idarubicin | QOL | First-line therapy | • ATRA and arsenic trioxide is a feasible treatment in low-risk and high-risk patients with acute promyelocytic leukemia, with a high cure rate and less relapse than, and survival not different to, ATRA and idarubicin. |
| Gemtuzumab ozogamicin (high-risk) + tretinoin (ATRA) + arsenic trioxide (ATO) | 2A | No | Phase 2 (ECOG S0535) | N/A | 3-year EFS | Newly diagnosed | • The combination of GO, ATRA, and ATO was effective in patients with high-risk APL, producing highly durable responses, low rates of early mortality, and comparing favorably with chemotherapy-based induction regimens in this setting. |

| Acute promyelocytic leukemia – first relapse | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Regimen** | **NCCN Category** | **FDA Approved** | **Trial Design** | **Comparator** | **Primary End-Point** | **Line of Therapy** | **Conclusion** |
| Gemtuzumab ozogamicin + arsenic trioxide (ATO) | 2A | No | Case study | N/A | ----- | Molecular relapsed disease | • In this study, 14 of 16 patients with APL in molecular relapse responded to treatment with GO. |
| Gemtuzumab ozogamicin (GO)+ tretinoin (ATRA) ± arsenic trioxide (ATO) | 2A | No | Case study | N/A | ----- | First relapse | • The combination of ATO, ATRA, and GO was effective and may achieve durable remissions in patients with APL in first recurrence with 6 out of 8 patients remaining alive and in CR after a median follow-up of more than 36 months. |