OVERVIEW
Mylotarg is an antibody-drug conjugate, consisting of a monoclonal antibody directed towards the human CD33 antigen, covalently linked to the cytotoxic agent, N-acetyl gamma calicheamicin. Upon binding of Mylotarg to the CD33 antigen, the antibody-drug conjugate is internalized by the cancerous cell and N-acetyl gamma calicheamicin is released intracellularly from the antibody where it causes breaks in double-stranded DNA leading to cell cycle arrest and apoptosis. The CD33 antigen is expressed on myeloid blasts in > 80% of acute myeloid leukemia (AML) patients.2,3

Mylotarg is indicated for the treatment of:
- Newly diagnosed CD33-positive AML in adults; AND
- Relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older.1

Guidelines
The National Comprehensive Cancer Network (NCCN) guidelines for Acute Myeloid Leukemia (version 3.2019 – May 7, 2019) recommend Mylotarg for induction therapy, post-remission therapy, and for relapsed/refractory CD33-positive AML.4,5 Mylotarg can be used as a single agent or in combination with cytarabine and daunorubicin. The NCCN guidelines for AML also recommend Mylotarg for induction and consolidation therapy of high-risk (white blood cell count > 10,000/µL) acute promyelocytic leukemia (APL), and for relapsed disease. Mylotarg can be used in combination with tretinoin and/or arsenic trioxide.

Acute Promyelocytic Leukemia – Dosing in First Morphologic or Molecular Relapse
In a pilot study, the safety and efficacy of Mylotarg in patients with APL in molecular relapse (N = 16) was assessed.6 Patients with two or more relapses, or those in the first relapse and not eligible for conventional chemotherapy were included in the study. Molecular relapse was defined as PML/RARα positivity, detected by reverse transcriptase-polymerase chain reaction with sensitivity of 10^-4, in two consecutive bone marrow samples collected any time after consolidation therapy in the absence of detectable blasts in the bone marrow or peripheral blood. Patients received Mylotarg 6 mg/m² and if the neutrophil and platelet counts had recovered to 1 x 10⁹/L and 100 x 10⁹/L, respectively a second dose was given 15 days later. If the counts had not recovered, the second dose was held until hematologic recovery. For patients who achieved molecular remission, a final (third) dose of 6 mg/m² was given. For patients still in relapse, Mylotarg 6 mg/m² was continued up to a maximum of 6 doses. Fourteen of 16 patients achieved molecular remission, seven patients achieved a sustained response lasting for a median of 15 months (range: 7 to 31 months) and seven patients relapsed between 3 and 15 months. Two of the relapsed patients were treated a second time with Mylotarg and achieved a new remission.

In a second pilot study, eight APL patients in first relapse were treated with arsenic trioxide, all-trans retinoic acid and Mylotarg.7 All patients had been previously treated with all-trans retinoic acid and chemotherapy. Relapse therapy included an induction phase which consisted of arsenic trioxide 0.15 mg/kg IV once daily (QD) until bone marrow remission and a consolidation phase which started once hematologic recovery occurred. Consolidation consisted of arsenic trioxide, all-trans retinoic acid and Mylotarg 9 mg/m² IV given once monthly for 10 months. After consolidation, patients received maintenance therapy which included idarubicin, all-trans retinoic acid, 6-mercaptopurine and methotrexate. Three patients completed consolidation, the other five patients received between two and seven cycles of consolidation. All patients
achieved CR, after a median of 36 months of follow-up, six patients were alive in CR and two died while in CR.

**POLICY STATEMENT**
Prior authorization is recommended for medical benefit coverage of Mylotarg. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In the case where approval is authorized in months, 1 month is equal to 30 days.

Due to the specialized skills required for evaluation and diagnosis of patients treated with Mylotarg, as well as the monitoring required for adverse events and long-term efficacy, approval requires Mylotarg to be prescribed by or in consultation with a physician who specializes in the condition being treated.

**RECOMMENDED AUTHORIZATION CRITERIA**
Coverage of Mylotarg is recommended in those who meet one of the following criteria:

**FDA-Approved Indications**

1. **Acute Myeloid Leukemia – Newly Diagnosed CD33-Positive.** Approve for 1 year if the patient meets the following criteria (A and B):
   - A) The patient is ≥ 18 years of age; AND
   - B) Mylotarg is prescribed by or in consultation with an oncologist.

   **Dosing.** Approve one of the following dosing regimens (A or B):
   - A) Combination therapy regimen (i, ii, and iii):
     - i. Each individual dose must not exceed 4.5 mg administered intravenously; AND
     - ii. Administer up to 3 doses of Mylotarg during the initial (induction) cycle; AND
     - iii. Administer 1 dose of Mylotarg during each subsequent (consolidation) cycle.¹
   - B) Single-agent regimen:
     - i. Each individual dose must not exceed 6 mg/m² administered intravenously; AND
     - ii. Administer up to 2 doses of Mylotarg during the initial (induction) cycle; AND
     - iii. Administer 1 dose no more frequently than once every 28 days during the subsequent (consolidation) phase.

   NOTE. Premedicate patients with acetaminophen, diphenhydramine and a corticosteroid prior to each dose of Mylotarg.¹ Acetaminophen and diphenhydramine can be repeated every 4 hours after the initial pretreatment dose. The corticosteroid can be repeated for any signs of an infusion reaction. Use appropriate measures to prevent tumor lysis syndrome. For patients with hyperleukocytosis (leukocyte count ≥ 30Gi/L), cytoreduction is recommended prior to Mylotarg administration.

2. **Acute Myeloid Leukemia – Relapsed or Refractory CD33-Positive.** Approve for 1 month if the patient meets the following criteria (A and B):
   - A) The patient is ≥ 2 years of age; AND
   - B) Mylotarg is prescribed by or in consultation with an oncologist;

   **Dosing.** Approve the following dosing regimen (A and B):
A) Each individual dose must not exceed 4.5 mg administered intravenously; AND
B) Administer no more than 3 doses of Mylotarg.

NOTE. Premedicate patients with acetaminophen, diphenhydramine and a corticosteroid prior to each dose of Mylotarg.¹ Acetaminophen and diphenhydramine can be repeated every 4 hours after the initial pretreatment dose. The corticosteroid can be repeated for any signs of an infusion reaction. Use appropriate measures to prevent tumor lysis syndrome. For patients with hyperleukocytosis (leukocyte count ≥ 30Gi/L), cytoreduction is recommended prior to Mylotarg administration.

Other Uses with Supportive Evidence

3. Acute Promyelocytic Leukemia – High-Risk. Approve for 6 months if the patient meets the following criteria (A, B, and C):
   A) The patient is ≥ 18 years of age; AND
   B) The patient has high risk disease, defined as a white blood cell count > 10,000/mcL; AND
   C) Mylotarg is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimen (A and B):
   A) Each individual dose of Mylotarg must not exceed 9 mg/m² administered intravenously; AND
   B) Mylotarg is administered no more frequently than once every 28 days.⁴

NOTE. Premedicate patients with acetaminophen, diphenhydramine and a corticosteroid prior to each dose of Mylotarg.¹ Acetaminophen and diphenhydramine can be repeated every 4 hours after the initial pretreatment dose. The corticosteroid can be repeated for any signs of an infusion reaction. Use appropriate measures to prevent tumor lysis syndrome. For patients with hyperleukocytosis (leukocyte count ≥ 30Gi/L), cytoreduction is recommended prior to Mylotarg administration.

4. Acute Promyelocytic Leukemia – First Relapse (Morphologic or Molecular). Approve for 6 months if the patient meets the following criteria (A and B):
   A) The patient is ≥ 2 years of age; AND
   B) Mylotarg is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimen (A and B):
   A) Each individual dose of Mylotarg must not exceed 9 mg/m² administered intravenously; AND
   B) Mylotarg is administered no more frequently than once every 28 days.⁶–⁹

NOTE. Premedicate patients with acetaminophen, diphenhydramine and a corticosteroid prior to each dose of Mylotarg.¹ Acetaminophen and diphenhydramine can be repeated every 4 hours after the initial pretreatment dose. The corticosteroid can be repeated for any signs of an infusion reaction. Use appropriate measures to prevent tumor lysis syndrome. For patients with hyperleukocytosis (leukocyte count ≥ 30Gi/L), cytoreduction is recommended prior to Mylotarg administration.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Mylotarg has not been shown to be effective or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)
1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

HISTORY

<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Policy</td>
<td>-</td>
<td>08/08/2018</td>
</tr>
<tr>
<td>Annual review</td>
<td>Revised approval duration for AML – Newly Diagnosed CD33-Positive to 1 year.</td>
<td>07/17/2019</td>
</tr>
<tr>
<td></td>
<td>Removed Initial/Extended Approval, Duration of Therapy, and Labs/Diagnostics sections from each indication.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Removed Waste Management and Other Cancer Indication sections.</td>
<td></td>
</tr>
</tbody>
</table>