PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Mylotarg™ (gemtuzumab ozogamicin for injection – Pfizer)

APPROVAL DATE: 07/17/2019

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.[1] 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 is 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/m^2 and if the neutrophil and platelet counts had recovered to 1 x 10^9/L and 100 x 10^9/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/m^2 was given. For patients still in relapse, Mylotarg 6 mg/m^2 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/m^2 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 prescription benefit coverage of Mylotarg. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mylotarg is recommended in those who meet 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.

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;

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 white blood cell count > 10,000/mcL; AND
   - **C)** Mylotarg is prescribed by or in consultation with an oncologist.

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.

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.

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

1. Mylotarg™ for intravenous infusion [prescribing information]. Philadelphia, PA: Pfizer; April 2018.
2. Daver N, Kantarjian H, Ravandi F, et al. A Phase II Study of Decitabine and Gemtuzumab Ozogamicin in Newly Diagnosed and Relapsed Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome. *Leukemia*. 2016;30:268-273.
3. O'Hear C, Heiber JF, Schubert I, Fey G, Geiger TL. Anti-CD33 Chimeric Antigen Receptor Targeting of Acute Myeloid Leukemia. *Haematologica*. 2015;100:336-344.
4. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 3.2019 – May 7, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2019.
5. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2019. Search term: gemtuzumab.
6. Lo-Coco F, Cimino G, Breccia M, et al. Gemtuzumab Ozogamicin (Mylotarg) as a Single Agent for Molecularly Relapsed Acute Promyelocytic Leukemia. *Blood*. 2004;104:1995-1999.
7. 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;109:1355-1359.
8. Schwarz J, Markova J, Pekova S, et al. A Single Administration of Gemtuzumab Ozogamicin for Molecular Relapse of Acute Promyelocytic Leukemia. *Hematol J*. 2004;5:279-280.
9. Tsimberidou AM, Estey E, Whitman GJ, et al. Extramedullary Relapse in a Patient with Acute Promyelocytic Leukemia: Successful Treatment with Arsenic Trioxide, all-*trans* Retinoic Acid and Gemtuzumab Ozogamicin Therapies. *Leuk Res*. 2004;28:991-994.