Reference number(s)
4373-A

Standard Medicare Part B Management Evomela

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Evomela	melphalan

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Evomela is indicated for use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.

Compendial Uses[2,3]

- Palliative treatment for multiple myeloma
- POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome
- Amyloidosis
- Bone marrow transplant
- Hodgkin's disease
- Ovarian cancer
- Melanoma
- Gastrointestinal adenocarcinoma

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- Retinoblastoma

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Multiple Myeloma[1,3]

Authorization of 12 months may be granted for treatment of multiple myeloma when used in one of the following settings:

- High-dose conditioning treatment prior to stem cell transplant.
- Palliative treatment of patients whom oral therapy is not appropriate.

POEMS[2]

Authorization of 12 months may be granted for management of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome when both of the following criteria are met:

- The member is transplant ineligible.
- The requested drug will be used in combination with dexamethasone.

Amyloidosis[3]

Authorization of 12 months may be granted for the treatment of amyloidosis.

Bone Marrow Transplant[3]

Authorization of 12 months may be granted for the bone marrow transplants when either of the following is met:

- The requested drug will be used as part of a conditioning regimen prior to allogenic stem cell transplantation in one of the following regimens:
  - In combination with busulfan.
  - In combination with carmustine, etoposide, and cytarabine.
  - In combination with a fludarabine regimen (e.g., fludarabine, cyclophosphamide, and antithymocyte globulin; fludarabine; or fludarabine, cytarabine and idarubicin).
- The requested drug will be used as a conditioning regimen prior to autologous bone marrow transplantation in combination with busulfan.

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Hodgkin's disease[3]

Authorization of 12 months may be granted for the treatment of Hodgkin's disease in combination with carmustine, etoposide, cytarabine and autologous hematopoietic stem cell transplant.

Ovarian cancer[3]

Authorization of 12 months may be granted for the palliative treatment of non-resectable malignant epithelial ovarian cancer when administered intraperitoneally.

Melanoma[3]

Authorization of 12 months may be granted for the treatment of melanoma if the disease is not metastatic.

Gastrointestinal Adenocarcinoma[3]

Authorization of 12 months may be granted for the treatment of gastrointestinal adenocarcinoma when administered intraperitoneally.

Retinoblastoma[3]

Authorization of 12 months may be granted for the treatment of retinoblastoma when either of the following are met:

- The requested drug will be administered as part of superselective ophthalmic artery chemotherapy in members undergoing primary or secondary treatment.
- The requested drug will be administered as an intravitreal injection for the treatment of vitreous seeds.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested drug.
- The requested drug is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen.

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Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Evomela
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service-Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Multiple myeloma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Evomela are covered in addition to the following:

- Palliative treatment for multiple myeloma
- POEMS syndrome
- Amyloidosis
- Bone marrow transplant
- Hodgkin's disease
- Ovarian cancer
- Melanoma
- Gastrointestinal adenocarcinoma
- Retinoblastoma

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Evomela as palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Evomela to treat POEMS syndrome can be found in the National Comprehensive Cancer Network's guideline for multiple myeloma. The NCCN Guideline for multiple myeloma supports the use of Evomela in combination with dexamethasone for transplant ineligible patients. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).Support for using Evomela to treat amyloidosis can be found in a study by Brown and Walls. Amyloidosis is often observed in patients with rheumatoid arthritis or multiple myeloma. Amyloidosis usually progresses

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slowly, with most patients surviving from 1 to 4 years (median, 14 months) following diagnosis. Melphalan (5 to 12 mg/day for 4 to 7 days repeated every 4 to 6 weeks) and prednisone therapy has been beneficial to patients with amyloidosis. Unfortunately, some patients treated with alkylating agents have developed acute leukemia.

Additionally, Moreau et al published a case report where high-dose melphalan and autologous bone marrow transplant (ABMT) induced prolonged survival and response in a patient with poor-prognosis AL amyloidosis. During a 5-month period, the patient had upper-body myasthenia, dyspnea, cardiomegaly and elevated creatine kinase. A biopsy confirmed gamma-type AL amyloidosis deposition. The patient was not treated initially, but because of rapid disease progression, ABMT was performed following intravenous melphalan 200 milligrams/square meter approximately 4 months later. At 12 months the patient was greatly improved and able to work. Serum remained negative for monoclonal gamma chains and proteinuria at 3, 6, 12, and 17 months after ABMT. Despite prolonged clinical remission, the patient had persistent left ventricular hypertrophy and amyloid deposition on endomyocardial biopsy.

Support for using Evomela to treat bone marrow transplant can be found in three studies. Van Besien et al published a paper on using melphalan as part of a conditioning regimen for allogenic transplant. High-dose melphalan-based chemotherapy allowed for durable engraftment of allogeneic bone marrow in 4 patients. Patients received conditioning regimens consisting of BEAM (carmustine, etoposide, cytarabine, melphalan) or busulfan plus melphalan. All 4 patients had prompt engraftment. Two patients had prolonged disease-free survival.

Anderlini, Giralt and Andersson reported on their experience with allogenic stem cell transplantation with fludarabine-based conditioning regimens. A successful engraftment was achieved in 4 of 5 evaluable patients with advanced Hodgkin's disease who received allogeneic stem cell transplantation (n=6; peripheral blood progenitor cell=4; bone marrow transplant=2) following a conditioning regimen of fludarabine, cyclophosphamide, and antithymocyte globulin (n=4), fludarabine and melphalan (n=1), or fludarabine, cytarabine, and idarubicin (n=1). Patients were heavily pretreated (median 7 chemotherapy regimens); all had received prior radiation therapy and had undergone a prior autologous bone marrow/stem cell transplant. Chimerism studies 30 days after transplantation showed 100% donor-derived hematopoiesis in 4 of 5 evaluable patients (4 of 4 responders). Ongoing 100% donor- derived chimerism which has lasted a minimum of 6 months was achieved in 3 of 3 responders. A pilot study (n=4) of a conditioning regimen included fludarabine (25 milligrams/square meter (mg/m(2))/day intravenously (IV) for 5 days), cyclophosphamide (1 gram (g)/m(2)/day IV for 3 days), and antithymocyte globulin (20 mg/kilogram/day IV for 3 days). One patient received fludarabine (25 mg/m(2)/day IV for 5 days) and melphalan (90 mg/m(2)/day IV for 2 days. One patient with a coexistent therapy-related myelodysplasia received fludarabine (30 mg/m(2)/day IV for 4 days), cytarabine (2 g/m(2)/day for 4 days), and idarubicin (12 mg/m(2)/day IV for 3 days) (FLAG-IDA). Cyclosporine or tacrolimus was administered IV beginning 2 days before transplantation and switched to oral administration when feasible. Methotrexate (5 mg/m(2) IV) was administered on days 1, 3, and 6 with an additional administration on day 11 for unrelated donor transplants. Patients received antibacterial, antifungal and antiviral prophylaxis. Day 100 transplant-related mortality was 2 of 6 patients (33%). Sibling-donor transplant related mortality was 25%. One patient died of intracerebral hemorrhage (day 48) with coexistent therapy-related myelodysplasia, one of viral pneumonia (day 63), and one of progressive disease (8 months) despite salvage chemotherapy and

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donor lymphocyte/stem cell infusions. Acute graft-versus-host disease (GVHD) developed in 4 of 6 patients; chronic GVHD responsive to steroid therapy developed in 2 of 4 evaluable patients. Regimen-related toxicity was mainly hepatic and gastrointestinal and was Grade 2 in 5 patients, Grade 1 in 1 patient.

Srivastave, Bradstock and Szer reported experience using busulfan plus melphalan as a safe and inexpensive conditioning regimen for autologous bone marrow transplantation (autologous BMT). Twenty-four patients with a variety of malignancies (lymphoma, myeloma, ALL, solid tumors) received oral busulfan 1 mg/kg every 6 hours on days (-)6 to (-)3 followed by melphalan 140 mg/m(2) on day (-2) (cryopreserved hemopoietic cells were administered on day 0). Sixteen evaluable patients had a complete remission following BMT with 8 patients remaining in complete remission 12 to 46 months (median of 29 months) later. Toxicity was acceptable (major toxicity was gastrointestinal). This combination had the greatest antitumor in lymphoma patients.

Support for using Evomela to treat Hodgkin's disease, ovarian cancer, melanoma, gastrointestinal adenocarcinoma and retinoblastoma can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Evomela [package insert]. East Windsor, NJ: Acrotech Biopharma LLC; June 2023.
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