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Reviewed: 08/09/23

Revised: 09/15/23

Subject: Melphalan HCl, Captisol-Enabled (Evomela®) IV Infusion

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DESCRIPTION:

Captisol-enabled melphalan hydrochloride (Evomela) is a propylene glycol -free injectable formulation of melphalan hydrochloride (HCl) that was approved by the US Food and Drug Administration (FDA) in March 2016 for use as a high-dose conditioning treatment prior to an autologous hematopoietic stem-cell transplant (HSCT) in patients with multiple myeloma (MM), and for the palliative treatment of patients with MM for whom oral therapy is not appropriate. Evomela was previously granted orphan drug designation by the FDA in November 2008 for "high dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation." Evomela is the first drug to be approved by the FDA for high-dose conditioning in MM. While considered an off-label use, standard melphalan HCl (Alkeran) has been a mainstay in high-dose conditioning in MM for decades. In August 2021, the manufacturer voluntarily removed the palliative treatment of multiple myeloma indication from the Evomela label.

Melphalan HCl is an alkylating agent first approved in 1964 for the palliative treatment of MM and, in addition to its myeloablative role prior to HSCT, it is also used for the treatment of certain other malignancies. Standard melphalan HCl is available as both an oral tablet and powder for injection that must be solubilized in a propylene glycol (PG) diluent. Each 10 mL vial of diluent contains 6 mL of PG. The reconstituted vial must be immediately diluted in normal saline for IV administration, and the IV administration completed within 60 minutes of reconstitution. This is because the solution is unstable. About 1% label strength of melphalan hydrolyzes every 10 minutes after dilution.

Captisol [a.k.a., sulfobutylether-beta-cyclodextrin (SBECD) and Betadex sulfobutyl ether sodium] is a patent-protected, chemically modified cyclodextrin with a structure designed to "optimize the solubility and stability of drugs". Captisol is currently used in various FDA-approved injectable products such as

carfilzomib (Kyprolis), PG-free amiodarone injection (Nexterone), and posaconazole injection (Noxafil). The use of Captisol in Evomela allows for a PG-free formulation of melphalan and enhanced stability. At room temperature, Evomela can be stored up to 1 hour after reconstitution and is stable for an additional 4 hours after preparation of the infusion solution. Stability studies have shown that the rate of degradation for reconstituted solutions of standard melphalan HCl in vials was 17-times faster than reconstituted Evomela, and 5-times faster in infusion bag admixtures. The manufacture claims that the improved stability of Evomela may potentially ensure that cancer patients receive the full, intended therapeutic dose of IV melphalan by increasing the use time and infusion time, and simplifying clinical administration logistics. The clinical benefit of Evomela being PG-free is unclear, especially considering the MM conditioning regimen is only two doses. Propylene glycol toxicity has been rarely reported in patients who are receiving high-dose continuous infusions of PG-containing medication such as benzodiazepines. There are no reports of PG toxicity resulting from IV melphalan administration.

The FDA-approval of Evomela for high-dose conditioning in MM was based on the results of a phase IIb, open-label, single-arm, non-randomized trial conducted at 5 US centers in 61 patients with symptomatic MM. Fifty-six patients had newly diagnosed disease and five patients had relapsed after stem cell transplant. Evomela was administered at 100 mg/m^2/day over 30 minutes by IV infusion for two consecutive days (Day -3 and Day -2) prior to autologous stem cell transplantation (ASCT) (Day 0). The objective of the trial was to determine the overall safety and toxicity profile of Evomela. The efficacy was evaluated by the International Myeloma Working Group response criteria comparing the disease response immediately prior to the ASCT procedure to the disease response assessed 90 to 100 days post-transplant. The overall response rate (partial response or better) improved from 79% (48 of 61) prior to the ASCT procedure to 95% (58 of 61) at 90 to 100 days post-transplant. There was also an increase in the number of patients with a stringent complete response from 0 patients prior to the ASCT procedure to 16% (10 of 61) at 90 to 100 days post-transplant. Myeloablation, neutrophil engraftment and platelet engraftment were achieved by all 61 patients.

The National Comprehensive Cancer Network (NCCN) does not specifically address the use of Captisol-enabled melphalan (Evomela) in any of its guidelines. The guidelines only reference “melphalan” in general. The NCCN guidelines and disease states that include IV melphalan are limited to relapsed/refractory systemic light chain amyloidosis, highly-refractory classic Hodgkin lymphoma, multiple myeloma, and various conditioning regimens for allogeneic and autologous stem cell transplantation.

POSITION STATEMENT:

Initiation of Captisol-enabled melphalan (Evomela) **meets the definition of medical necessity** when **BOTH** of the following criteria are met:

1. The member will be receiving Evomela as a conditioning treatment prior to a hematopoietic progenitor (stem) cell transplantation (HSCT)
2. The dosage of Evomela does **NOT** exceed the following:
    a. 100 mg/m^2/day for 2 consecutive days or 200 mg/m^2 as a single dose prior to HSCT

b. For members who weigh more than 130% of their ideal body weight (IBW), body surface area (BSA) should be calculated based on adjusted ideal body weight (ABW) [ABW=IBW+0.4(actual weight-IBW)]

Approval duration: single one-time approval of up to 200 mg/m^2

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

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

The recommended dose is 100 mg/m^2/day administered over 30 minutes by intravenous infusion for 2 consecutive days (Day -3 and Day -2) prior to autologous stem cell transplantation (ASCT, Day 0).

For patients who weigh more than 130% of their ideal body weight, body surface area (BSA) should be calculated based on adjusted ideal body weight.

Dose Adjustments

- Renal Impairment: No dose adjustment is necessary.
- Hepatic Impairment: Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.

Drug Availability

- 50 mg of lyophilized powder in a single-dose vial for reconstitution. Each vial contains 50 mg melphalan free base equivalent to 56 mg melphalan hydrochloride. Evomela is light sensitive and must be retained in the original carton until use.

PRECAUTIONS:

Boxed Warning

WARNING: SEVERE BONE MARROW SUPPRESSION, HYPERSENSITIVITY, AND LEUKEMOGENICITY

- Severe bone marrow suppression with resulting infection or bleeding may occur. Controlled trials comparing intravenous (IV) melphalan to oral melphalan have shown more myelosuppression with the IV formulation. Monitor hematologic laboratory parameters.
- Hypersensitivity reactions, including anaphylaxis, have occurred in approximately 2% of patients who received the IV formulation of melphalan. Discontinue treatment with Evomela for serious hypersensitivity reactions.

- Melphalan produces chromosomal aberrations in vitro and in vivo. Evomela should be considered potentially leukemogenic in humans.

Contraindications

- History of serious allergic reaction to melphalan

Precautions/Warnings

- Bone Marrow Suppression: See Boxed Warning
- Gastrointestinal Toxicity: Nausea, vomiting, diarrhea or oral mucositis may occur; provide supportive care using antiemetic and antidiarrheal medications as needed. Prophylactic antiemetics should be administered. Provide nutritional support and analgesics for patients with severe mucositis.
- Hepatotoxicity: Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice have been reported after treatment with melphalan. Hepatic veno-occlusive disease has also been reported. Monitor liver chemistries
- Hypersensitivity: See Boxed Warning
- Secondary Malignancies: See Boxed Warning
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to fetus and to avoid pregnancy
- Infertility: Melphalan may cause ovarian function suppression or testicular suppression

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9246	Injection, melphalan (evomela), 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

C00.0 – D49	Neoplasms
Z94.81	Bone marrow transplant status
Z94.84	Stem cells transplant status

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

Allogeneic Hematopoietic Cell Transplantation, 02-38240-01
Autologous Hematopoietic Cell Transplantation, 02-38241-01

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 08/09/23.

GUIDELINE UPDATE INFORMATION:

06/15/16	New Medical Coverage Guideline.
07/15/17	Review and revision to guidelines consisting of updating the position statement to only include use as a high-dose conditioning treatment prior to stem cell transplantation for treatment of MM. The NCCN no longer recommends melphalan as part of any MM treatment regimen.
07/01/20	Revision: Added HCPCS code J9246 and deleted code J9245.
09/15/23	Review and revision to guidelines consisting of updating the position statement to allow the use of Evomela as conditioning treatment prior to a stem cell transplantation regardless of the underlying disease being treated. Updated the maximum dosage to provide flexibility based on the conditioning regimen used. Updated description, dosage/administration, billing/coding, related guidelines, definitions, and references.