RECONSTITUTION GUIDE

Evomela®. Stable by Design.

Indications and Usage

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

Important Safety Information

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.**

Please see additional Important Safety Information on pages 2-4.

Please see accompanying full Prescribing Information or visit www.evomela.com/PI for full Prescribing Information.

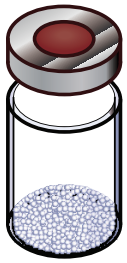
Evomela®
(melphalan) for Injection
50 mg per vial

RECOMMENDED DOSAGE FOR CONDITIONING TREATMENT

- The recommended dose of Evomela® for conditioning treatment 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 should be calculated based on adjusted ideal body weight
- Administer prophylactic antiemetics to address gastrointestinal toxicity such as nausea and vomiting that can occur when administering Evomela®

HOW SUPPLIED

- Evomela® is supplied in a single carton containing one (1) vial. Each 50 mg vial contains a white to off-white lyophilized powder in a single-dose vial for reconstitution. (After reconstitution, the solution is clear and colorless to light yellow)
- Each vial contains 50 mg melphalan free base equivalent to 56 mg melphalan hydrochloride
- NDC 72893-001-01: Individual carton of Evomela® 20 mL single-dose vial containing 50 mg melphalan free base



Evomela®
50 mg per vial
lyophilized powder

STORAGE AND HANDLING

- Store Evomela® at room temperature 25°C (77°F)
- Temperature excursions are permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]
- Evomela® is light sensitive
- Retain in original carton until use
- Melphalan is a hazardous drug
- Follow applicable special handling and disposal procedures

Select Important Safety Information

Evomela® (melphalan) for Injection 50 mg per vial

Contraindications

History of serious allergic reaction to melphalan.

Warnings and Precautions

- **Bone Marrow Suppression:** For patients receiving Evomela® as part of a conditioning regimen, myeloablation occurs in all patients. Do not begin the conditioning regimen if a stem cell product is not available for rescue. Monitor complete blood counts, provide supportive care for infections, anemia and thrombocytopenia until there is adequate hematopoietic recovery.
- **Gastrointestinal Toxicity:** For patients receiving Evomela® as part of a conditioning regimen, nausea, vomiting, mucositis, and diarrhea may occur in over 50% of patients. Use prophylactic antiemetic medication. Provide supportive care for nausea, vomiting, diarrhea, and mucositis. The frequency of grade 3/4 mucositis in clinical studies was 13%. 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.

RECONSTITUTION AND INFUSION INSTRUCTIONS

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

1. Use normal saline solution (0.9% sodium chloride injection, USP) (8.6 mL as directed) to reconstitute Evomela® and make a 50 mg/10 mL (5 mg/mL) nominal concentration of melphalan.

2. Calculate the required volume of Evomela® needed for a patient's dose and withdraw that volume from the vial(s).

3. Add the required volume of Evomela® to the appropriate volume of 0.9% sodium chloride injection, USP to a final concentration of 0.45 mg/mL.

4. Infuse over 30 minutes via an injection port or central venous catheter.

- The reconstituted Evomela® drug product is stable for 24 hours at refrigerated temperature (5°C/41°F) without any precipitation due to the high solubility
- The reconstituted Evomela® drug product is stable for 1 hour at room temperature

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- The Evomela® admixture solution is stable for 4 hours at room temperature in addition to the 1 hour following reconstitution

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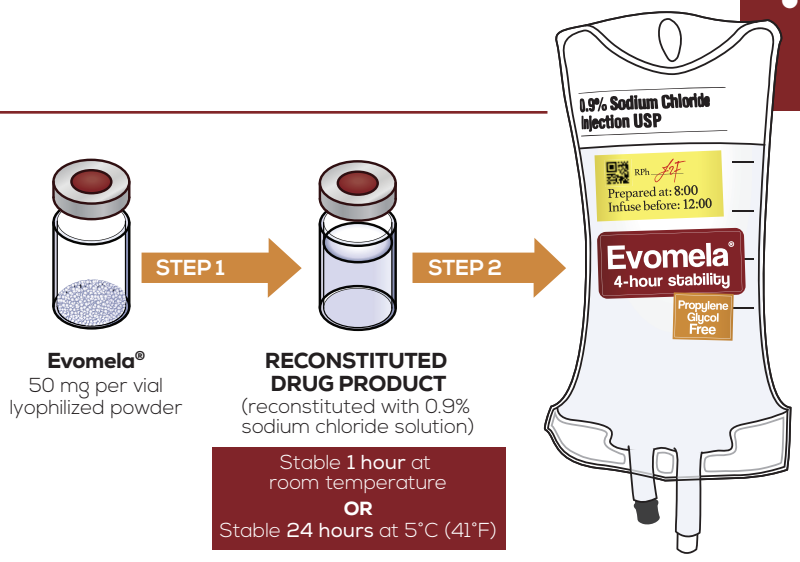
- Evomela® may cause local tissue damage should extravasation occur. Do not administer by direct injection into a peripheral vein
- Administer Evomela® by injecting slowly into fast-running IV infusion via a central venous access line



Evomela®
50 mg per vial
lyophilized powder

RECONSTITUTED DRUG PRODUCT
(reconstituted with 0.9% sodium chloride solution)

Stable **1 hour** at room temperature
OR
Stable **24 hours** at 5°C (41°F)

ADMIXTURE
(admix with 0.9% sodium chloride solution)

Stable **4 hours** at room temperature

ADMINISTRATION RECOMMENDATIONS
Infuse over 30 minutes for conditioning treatment

Select Important Safety Information

Evomela® (melphalan) for Injection
50 mg per vial

Warnings and Precautions continued

- **Hypersensitivity:** Acute hypersensitivity reactions, including anaphylaxis, have occurred in approximately 2% of patients who received an intravenous formulation of melphalan. Symptoms may include urticaria, pruritus, edema, and skin rashes and, in some patients, tachycardia, bronchospasm, dyspnea, and hypotension. Discontinue treatment with Evomela® for serious hypersensitivity reactions.

Select Important Safety Information

Warnings and Precautions continued

- **Secondary Malignancies:** Melphalan has been shown to cause chromatid or chromosome damage in humans. Secondary malignancies such as myeloproliferative syndrome or acute leukemia have been reported in multiple myeloma patients treated with melphalan-containing chemotherapy regimens. The potential benefit of Evomela® therapy must be considered against the possible risk of the induction of a secondary malignancy.
- **Embryo-Fetal Toxicity:** Based on its mechanism of action, Evomela® can cause fetal harm when administered to a pregnant woman. Melphalan is genotoxic, targets actively dividing cells, and was embryolethal and teratogenic in rats. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Evomela® and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Evomela® and for 3 months after the last dose.
- **Infertility:** Melphalan-based chemotherapy regimens have been reported to cause suppression of ovarian function in premenopausal women, resulting in persistent amenorrhea in approximately 9% of patients. Reversible or irreversible testicular suppression has also been reported.

Adverse Events

- The most common adverse reactions observed in at least 50% of patients with multiple myeloma treated with Evomela® were neutrophil count decreased, white blood cell count decreased, lymphocyte count decreased, platelet count decreased, diarrhea, nausea, fatigue, hypokalemia, anemia, and vomiting.
- For myeloablative conditioning in multiple myeloma patients undergoing ASCT, twelve (20%) patients experienced a treatment emergent serious adverse reaction while on study. The most common serious adverse reactions (>1 patient, 1.6%) were pyrexia, hematochezia, febrile neutropenia, and renal failure. Treatment-related serious adverse reactions reported in >1 patient were pyrexia (n=2, 3%), febrile neutropenia (n=2, 3%), and hematochezia (n=2, 3%).

Drug Interactions

- No formal drug interaction studies have been conducted. The development of severe renal impairment has been reported in patients treated with a single dose of intravenous melphalan 140-250 mg/m^2 followed by standard oral doses of cyclosporine. Intravenous melphalan may also reduce the threshold for BCNU lung toxicity.

Use in Specific Populations

- **Lactation:** It is not known whether melphalan is present in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing children from melphalan, breastfeeding is not recommended during treatment with Evomela® and for 1 week after the last dose.

Please see full Prescribing Information, including BOXED WARNING, at www.evomela.com/PI.

Reference

Evomela® [Prescribing Information], Acrotech Biopharma Inc.

EVO-0254