

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EVOMELA safely and effectively. See full prescribing information for EVOMELA.

EVOMELA (melphalan) for injection, for intravenous use

Initial U.S. Approval: 1964

WARNING: SEVERE BONE MARROW SUPPRESSION, HYPERSENSITIVITY, and LEUKEMOGENICITY

See full prescribing information for complete boxed warning.

- 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. (5.1)
- 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. (5.4)
- Melphalan produces chromosomal aberrations *in vitro* and *in vivo*. Evomela should be considered potentially leukemogenic in humans. (5.5)

INDICATIONS AND USAGE

Evomela is an alkylating drug indicated for:

- use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma. (1.1)
- the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate. (1.2)

DOSAGE AND ADMINISTRATION

- For **Conditioning Treatment**, the recommended dose of Evomela is 100 mg/m²/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). (2.1)
- For **Palliative Treatment**, the recommended dose of Evomela is 16 mg/m² administered as a single intravenous infusion over 15-20 minutes at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals. (2.2)

DOSAGE FORMS AND STRENGTHS

For Injection: 50 mg per vial, lyophilized powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

History of serious allergic reaction to melphalan

WARNINGS AND PRECAUTIONS

- Gastrointestinal toxicity: Nausea, vomiting, diarrhea or oral mucositis may occur; provide supportive care using antiemetic and antidiarrheal medications as needed. (2.1, 5.2)
- Embryo-fetal toxicity: Can cause fetal harm. Advise of potential risk to fetus and to avoid pregnancy. (5.6, 8.1, 8.3)
- Infertility: Melphalan may cause ovarian function suppression or testicular suppression. (5.7)

ADVERSE REACTIONS

Most common adverse reactions observed in at least 50% of patients treated with Evomela are neutrophil count decreased, white blood cell count decreased, lymphocyte count decreased, platelet count decreased, diarrhea, nausea, fatigue, hypokalemia, anemia, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Spectrum Pharmaceuticals, Inc. at 1-888-292-9617 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- *Nursing mothers*: Advise women against breastfeeding while being treated with Evomela. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: 03/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SEVERE BONE MARROW SUPPRESSION, HYPERSENSITIVITY, AND LEUKEMOGENICITY

1 INDICATIONS AND USAGE

- 1.1 Multiple Myeloma-Conditioning Treatment
- 1.2 Multiple Myeloma-Palliative Treatment

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage for Conditioning Treatment
- 2.2 Recommended Dosage for Palliative Treatment
- 2.3 Dose Modification for Renal Impairment
- 2.4 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Bone Marrow Suppression
- 5.2 Gastrointestinal Toxicity
- 5.3 Hepatotoxicity
- 5.4 Hypersensitivity
- 5.5 Secondary Malignancies
- 5.6 Embryo-Fetal Toxicity
- 5.7 Infertility

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients with Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Myeloablative Conditioning in Patients with Multiple Myeloma Undergoing ASCT
- 14.2 Palliative Treatment of Patients with Multiple Myeloma

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

1 FULL PRESCRIBING 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. [*see Warnings and Precautions (5.1)*]
- 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. [*see Warnings and Precautions (5.4)*]
- Melphalan produces chromosomal aberrations *in vitro* and *in vivo*. Evomela should be considered potentially leukemogenic in humans. [*see Warnings and Precautions (5.5)*]

2

3 1 INDICATIONS AND USAGE

4 1.1 Multiple Myeloma-Conditioning Treatment

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

7

8 1.2 Multiple Myeloma-Palliative Treatment

9 Evomela is indicated for the palliative treatment of patients with multiple myeloma for whom oral therapy is not
10 appropriate.

11

12 2 DOSAGE AND ADMINISTRATION

13 2.1 Recommended Dosage for Conditioning Treatment

14 The recommended dose of Evomela for conditioning treatment is 100 mg/m²/day administered over 30 minutes
15 by intravenous infusion for 2 consecutive days (Day -3 and Day -2) prior to autologous stem cell transplantation
16 (ASCT, Day 0). For patients who weigh more than 130% of their ideal body weight, body surface area should
17 be calculated based on adjusted ideal body weight.

18

19 Administer prophylactic antiemetics [*see Warnings and Precautions (5.2)*].

20

21 2.2 Recommended Dosage for Palliative Treatment

22 The recommended dose of Evomela for palliative treatment is 16 mg/m² administered as a single intravenous
23 infusion over 15-20 minutes at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at
24 4-week intervals.

25

26 Administer prophylactic anti-emetics [*see Warnings and Precautions (5.2)*].

27

28 2.3 Dose Modification for Renal Impairment

29

30 For Conditioning Treatment: No dose adjustment is necessary.

31

32 For Palliative Treatment: Dosage reduction of up to 50% should be considered in patients with renal impairment
33 (BUN ≥30 mg/dL) [*see Use in Specific Populations (8.6)*].

34

35 **2.4 Preparation and Administration**

36 Evomela is a cytotoxic drug. Follow applicable special handling and disposal procedures¹.

37
38 Evomela is light sensitive. Retain in original carton until use.

39
40 Do not mix Evomela with other melphalan hydrochloride for injection drug products.

41 42 Reconstitution and Infusion Instructions:

43
44 1. Use normal saline solution (0.9% Sodium Chloride Injection, USP) (8.6 mL as directed) to reconstitute
45 Evomela and make a 50 mg/10 mL (5 mg/mL) nominal concentration of melphalan. The normal saline used
46 to reconstitute each vial should appear to be assisted or pulled into the vial by the negative pressure (partial
47 vacuum) present in the vial. Discard any vial (and replace with another vial) if there is no vacuum present
48 when reconstituting the vial with normal saline.

49
50 The reconstituted Evomela drug product is stable for 24 hours at refrigerated temperature (5°C) without any
51 precipitation due to the high solubility.

52
53 The reconstituted Evomela drug product is stable for 1 hour at room temperature.

54
55 2. Calculate the required volume of Evomela needed for a patient's dose and withdraw that volume from the
56 vial(s).

57
58 3. Add the required volume of Evomela to the appropriate volume of 0.9% Sodium Chloride Injection, USP to
59 a final concentration of 0.45 mg/mL.

60
61 The Evomela admixture solution is stable for 4 hours at room temperature in addition to the 1 hour
62 following reconstitution.

63
64 4. Infuse over 30 minutes via an injection port or central venous catheter.

65
66 Evomela may cause local tissue damage should extravasation occur. Do not administer by direct injection into a
67 peripheral vein. Administer Evomela by injecting slowly into a fast-running IV infusion via a central venous
68 access line.

69
70 Parenteral drug products should be inspected visually for particulate matter and discoloration prior to
71 administration, whenever solution and container permit.

72 73 **3 DOSAGE FORMS AND STRENGTHS**

74 For injection: 50 mg, white to off-white lyophilized powder in single-dose vial for reconstitution (after
75 reconstitution the solution is clear and colorless to light yellow). Each vial contains 50 mg melphalan free base
76 equivalent to 56 mg melphalan hydrochloride.

77 78 **4 CONTRAINDICATIONS**

79 History of serious allergic reaction to melphalan.

80 81 **5 WARNINGS AND PRECAUTIONS**

82 **5.1 Bone Marrow Suppression**

83 For patients receiving Evomela as part of a conditioning regimen, myeloablation occurs in all patients. Do not
84 begin the conditioning regimen if a stem cell product is not available for rescue. Monitor complete blood

85 counts, provide supportive care for infections, anemia and thrombocytopenia until there is adequate
86 hematopoietic recovery.

87
88 For patients receiving Evomela as palliative treatment, if the bone marrow has been compromised by prior
89 irradiation, prior chemotherapy or is recovering from chemotherapy, the risk of severe myelosuppression with
90 Evomela is increased. Perform periodic complete blood counts during the course of treatment with Evomela.
91 Provide supportive care for infections, bleeding, and symptomatic anemia [see *Adverse Reactions (6.1)*].

92 93 **5.2 Gastrointestinal Toxicity**

94 For patients receiving Evomela as part of a conditioning regimen, nausea, vomiting, mucositis, and diarrhea
95 may occur in over 50% of patients. Use prophylactic antiemetic medication. Provide supportive care for nausea,
96 vomiting, diarrhea, and mucositis. The frequency of grade 3/4 mucositis in clinical studies was 13%. Provide
97 nutritional support and analgesics for patients with severe mucositis. [see *Dosage and Administration (2.1)* and
98 *Adverse Reactions (6.1)*].

99
100 For patients receiving Evomela as palliative treatment, nausea and vomiting, diarrhea, and oral ulceration may
101 occur. Use prophylactic antiemetics. Provide supportive care for nausea, vomiting, diarrhea and mucositis.

102 103 **5.3 Hepatotoxicity**

104 Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and
105 jaundice have been reported after treatment with melphalan. Hepatic veno-occlusive disease has also been
106 reported. Monitor liver chemistries.

107 108 **5.4 Hypersensitivity**

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

113 114 **5.5 Secondary Malignancies**

115 Melphalan has been shown to cause chromatid or chromosome damage in humans. Secondary malignancies
116 such as myeloproliferative syndrome or acute leukemia have been reported in multiple myeloma patients treated
117 with melphalan-containing chemotherapy regimens. The potential benefit of Evomela therapy must be
118 considered against the possible risk of the induction of a secondary malignancy.

119 120 **5.6 Embryo-Fetal Toxicity**

121 Based on its mechanism of action, Evomela can cause fetal harm when administered to a pregnant woman.
122 Melphalan is genotoxic, targets actively dividing cells, and was embryo-lethal and teratogenic in rats. Advise
123 females of reproductive potential to avoid pregnancy during and after treatment with Evomela. If this drug is
124 used during pregnancy or if the patient becomes pregnant while taking this drug, advise the patient of potential
125 risk to the fetus [see *Use in Specific Populations (8.1, 8.3)*].

126 127 **5.7 Infertility**

128 Melphalan-based chemotherapy regimens have been reported to cause suppression of ovarian function in
129 premenopausal women, resulting in persistent amenorrhea in approximately 9% of patients. Reversible or
130 irreversible testicular suppression has also been reported [see *Use in Specific Populations (8.3)*].

131 132 **6 ADVERSE REACTIONS**

133 The following serious adverse reactions are described in more detail in other sections of the prescribing
134 information.

- 135 • Bone Marrow Suppression [see *Warnings and Precautions (5.1)*]

- 136 • Gastrointestinal Toxicity [see Warnings and Precautions (5.2)]
- 137 • Hepatotoxicity [see Warnings and Precautions (5.3)]
- 138 • Hypersensitivity [see Warnings and Precautions (5.4)]
- 139 • Secondary Malignancies [see Warnings and Precautions (5.5)]

140

141 **6.1 Clinical Trials Experience**

142 Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the
 143 clinical studies of Evomela may not reflect the rates observed in practice.

144

145 The most common adverse reactions observed in at least 50% of patients with multiple myeloma treated with
 146 Evomela were neutrophil count decreased, white blood cell count decreased, lymphocyte count decreased,
 147 platelet count decreased, diarrhea, nausea, fatigue, hypokalemia, anemia, and vomiting.

148

149 Myeloablative Conditioning in Multiple Myeloma Patients Undergoing ASCT

150 The safety of Evomela was evaluated in 61 patients with multiple myeloma in a single arm clinical trial in
 151 which patients were administered Evomela at a dosage of 100 mg/m²/day administered over ~30 minutes
 152 (range: 24-48 minutes) by intravenous (IV) infusion for 2 consecutive days (Day -3 and Day -2) prior to
 153 autologous stem cell transplant (ASCT, Day 0).

154

155 Table 1 summarizes the adverse reactions from the single-arm trial in patients with multiple myeloma. Severe
 156 myelosuppression is expected and these adverse reactions are not listed below.

157

158 **Table 1: Non-hematologic Adverse Reactions in ≥ 25% of Patients with Multiple Myeloma Who**
 159 **Received Evomela Conditioning for ASCT**

160

Adverse Reactions	Number (%) of Patients (N 61)	
	All Grades	Grade 3 or 4
All Adverse Reactions	61	61
Diarrhea	57 (93%)	2 (3%)
Nausea	55 (90%)	1 (2%)
Fatigue	47 (77%)	1 (2%)
Hypokalemia	45 (74%)	17 (28%)
Vomiting	39 (64%)	0 (0%)
Hypophosphatemia	30 (49%)	29 (48%)
Decreased Appetite	30 (49%)	0 (0%)
Pyrexia	29 (48%)	2 (3%)
Constipation	29 (48%)	0 (0%)
Febrile Neutropenia	25 (41%)	17 (28%)
Mucosal Inflammation	23 (38%)	6 (10%)
Dizziness	23 (38%)	0 (0%)
Edema Peripheral	20 (33%)	0 (0%)
Stomatitis	17 (28%)	3 (5%)
Abdominal Pain	17 (28%)	0 (0%)
Dysgeusia	17 (28%)	0 (0%)
Dyspepsia	16 (26%)	0 (0%)

161

162

163 ***Serious Adverse Reactions***

164 Twelve (20%) patients experienced a treatment emergent serious adverse reaction while on study. The most
165 common serious adverse reactions (>1 patient, 1.6%) were pyrexia, hematochezia, febrile neutropenia, and renal
166 failure. Treatment-related serious adverse reactions reported in >1 patient were pyrexia (n=2, 3%), febrile
167 neutropenia (n=2, 3%), and hematochezia (n=2, 3%).

168 169 ***Palliative Treatment of Patients with Multiple Myeloma***

170 The safety of melphalan was evaluated in 295 patients with multiple myeloma in the randomized clinical trial.
171 One hundred and ninety-five patients were administered IV melphalan at a dosage of 16 mg/m² q 2 weeks x 4
172 (over 6 weeks) followed by the same dose every 4 weeks. One hundred patients were administered oral
173 melphalan at a dosage of 0.15 mg/kg/day x 7 followed by 0.05 mg/kg/day when WBC counts began to rise.

174
175 Severe myelotoxicity (WBC ≤1,000 and/or platelets ≤25,000) was more common in the IV melphalan arm
176 (28%) than in the oral melphalan arm (11%).

177
178 An association was noted between poor renal function and myelosuppression; consequently, an amendment to
179 the protocol required a 50% reduction in IV melphalan dose if the BUN was ≥30 mg/dL. The rate of severe
180 leukopenia in the IV arm in the patients with BUN over 30 mg/dL decreased from 50% (8/16) before protocol
181 amendment to 11% (3/28) after the amendment.

182
183 Before the dosing amendment, there was a 10% (8/77) incidence of drug-related death in the IV arm. After the
184 dosing amendment, this incidence was 3% (3/108). This compares to an overall 1% (1/100) incidence of drug-
185 related death in the oral melphalan arm.

186 187 **7 DRUG INTERACTIONS**

188 No formal drug interaction studies have been conducted. The development of severe renal impairment has been
189 reported in patients treated with a single dose of intravenous melphalan 140-250 mg/m² followed by standard
190 oral doses of cyclosporine. Intravenous melphalan may also reduce the threshold for BCNU lung toxicity. When
191 nalidixic acid and IV melphalan are given simultaneously, the incidence of severe hemorrhagic necrotic
192 enterocolitis has been reported to increase in pediatric patients.

193 194 **8 USE IN SPECIFIC POPULATIONS**

195 **8.1 Pregnancy**

196 197 *Risk Summary*

198 Based on its mechanism of action, Evomela can cause fetal harm when administered to a pregnant woman,
199 including teratogenicity and/or embryo-fetal lethality. Melphalan is a genotoxic drug and can cause chromatid
200 or chromosome damage in humans [*see Nonclinical Toxicology (13.1)*]. In animal studies, melphalan was
201 embryo-lethal and teratogenic in rats at doses below the recommended clinical doses [*see Data*]. Advise a
202 pregnant woman of the potential risk to a fetus.

203
204 The background risk of major birth defects and miscarriage for the indicated populations are unknown.
205 However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage
206 is 15-20% of clinically recognized pregnancies.

207 208 Data

209 210 *Animal Data*

211 Adequate animal studies have not been conducted with intravenous melphalan. Melphalan was embryo-lethal
212 and teratogenic in rats following oral administration of 6 to 18 mg/m²/day for 10 days (0.06 to 0.18 times the
213 highest recommended clinical dose of 100 mg/m²/day) and intraperitoneal administration of 18 mg/m² (0.18

214 times the highest recommended clinical dose). Malformations resulting from melphalan administration included
215 alterations of the brain (underdevelopment, deformation, meningocele, and encephalocele) and eye
216 (anophthalmia and microphthalmos), reduction of the mandible and tail, and hepatocele (exomphaly).

217

218 **8.2 Lactation**

219

220 *Risk Summary*

221 It is not known whether melphalan is present in human milk. Because many drugs are excreted in human milk
222 and because of the potential for serious adverse reactions in nursing infants from melphalan, breastfeeding is
223 not recommended during treatment with Evomela.

224

225 **8.3 Females and Males of Reproductive Potential**

226

227 Contraception

228

229 Females

230 Evomela administration can cause fetal harm when administered to a pregnant woman. Advise females of
231 reproductive potential to avoid pregnancy, which may include the use of effective contraception methods,
232 during and after treatment with Evomela.

233

234 Males

235 Evomela administration may damage spermatozoa and testicular tissue, resulting in possible genetic fetal
236 abnormalities. Advise males with female sexual partners of reproductive potential to use effective contraception
237 during and after treatment with Evomela [see *Nonclinical Toxicology (13.1)*].

238

239 Infertility

240

241 Females

242 Melphalan causes suppression of ovarian function in premenopausal women, resulting in amenorrhea in a
243 significant number of patients.

244

245 Males

246 Reversible and irreversible testicular suppression has been reported in male patients after administration of
247 melphalan.

248

249 **8.4 Pediatric Use**

250 Pediatric patients were not included in clinical trials. Safety and effectiveness have not been established in
251 pediatric patients.

252

253 **8.5 Geriatric Use**

254 Of the total number of subjects in the single-arm pivotal study of Evomela, 30% were 65 and over, but no
255 patients were 75 and over. No overall differences in safety or effectiveness were observed between these
256 subjects and younger subjects. A greater incidence of engraftment syndrome was observed in older patients; 7%
257 (3 of 43) of patients younger than 65 years old versus 28% (5 of 18) of patients 65 years old and over.

258

259 **8.6 Patients with Renal Impairment**

260

261 For Conditioning Treatment, renal impairment is not a criterion for dose reduction or exclusion from Evomela
262 therapy.

263

264 For Palliative Treatment, consider dose reduction for patients with renal impairment receiving Evomela. Bone
265 marrow suppression has been observed in patients with BUN levels ≥ 30 mg/dL. A 50% reduction in the IV

266 melphalan dose decreased the incidence of severe bone marrow suppression in the latter portion of this study
267 [see Dosage and Administration (2.3)].

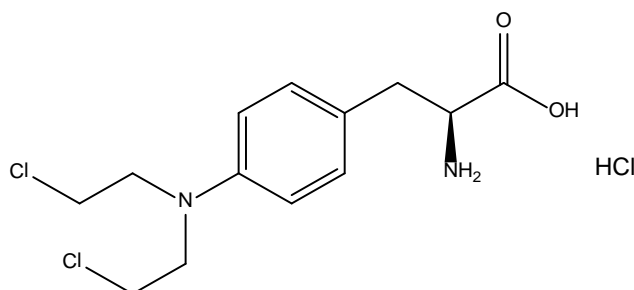
268 269 **10 OVERDOSAGE**

270 Overdoses resulting in death have been reported with melphalan. Overdoses, including doses up to 290 mg/m²,
271 have produced the following symptoms: severe nausea and vomiting, decreased consciousness, convulsions,
272 muscular paralysis, and cholinomimetic effects. Severe mucositis, stomatitis, colitis, diarrhea, and hemorrhage
273 of the gastrointestinal tract occur at high doses (>100 mg/m²). Elevations in liver enzymes and veno-occlusive
274 disease occur infrequently. Significant hyponatremia, caused by an associated inappropriate secretion of ADH
275 syndrome, has been observed. Nephrotoxicity and adult respiratory distress syndrome have been reported rarely.
276

277 The principal toxic effect is bone marrow suppression leading to leucopenia, thrombocytopenia and anemia.
278 Hematologic parameters should be closely followed for 3 to 6 weeks. An uncontrolled study suggests that
279 administration of autologous bone marrow or hematopoietic growth factors (i.e., sargramostim, filgrastim) may
280 shorten the period of pancytopenia. General supportive measures together with appropriate blood transfusions
281 and antibiotics should be instituted as deemed necessary by the physician. This drug is not removed from
282 plasma to any significant degree by hemodialysis or hemoperfusion. A pediatric patient survived a 254 mg/m²
283 overdose treated with standard supportive care.
284

285 **11 DESCRIPTION**

286 Evomela contains melphalan hydrochloride, an alkylating drug, as the active ingredient. The chemical name of
287 melphalan hydrochloride is 4-[bis(2-chloroethyl)amino]-L-phenylalanine hydrochloride. Its molecular formula
288 is C₁₃H₁₈Cl₂N₂O₂ • HCl and the molecular weight is 341.67. The structural formula is:
289



290
291 Melphalan hydrochloride is a white to off-white powder, with a melting range of 199°C – 201°C. It is
292 practically insoluble in water, but freely soluble in 1 N HCl and methanol.
293

294 Evomela (melphalan) for injection is supplied as a sterile white to off-white lyophilized powder in a single-dose
295 vial for intravenous use. Each vial contains 50 mg melphalan free base equivalent to 56 mg melphalan
296 hydrochloride and 2700 mg Betadex Sulfobutyl Ether Sodium, NF.
297

298 **12 CLINICAL PHARMACOLOGY**

299 **12.1 Mechanism of Action**

300 Melphalan is an alkylating agent of the bischloroethylamine type. As a result, its cytotoxicity appears to be
301 related to the extent of its interstrand cross-linking with DNA, probably by binding at the N⁷ position of
302 guanine. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor
303 cells.
304

305 **12.2 Pharmacodynamics**

306 *Cardiac Electrophysiology*

307 Pharmacokinetic-pharmacodynamic analysis showed that Evomela administration increased heart rate-corrected
308 QT interval. The mean change from baseline for QTcF at the mean C_{max} of 4701 ng/mL was 8.0 msec. Patients
309 treated with 200 mg/m² Evomela showed an increase of heart rate (mean change of 7.5 bpm from baseline).

311 **12.3 Pharmacokinetics**

312 Following injection, drug plasma concentrations declined rapidly in a biexponential manner with distribution
313 phase and terminal elimination phase half-lives of approximately 10 and 75 minutes, respectively. Estimates of
314 average total body clearance (CL) varied among studies, but typical values of approximately 7 to 9 mL/min/kg
315 (250 to 325 mL/min/m²) were observed. One study reported that on repeat dosing of 0.5 mg/kg every 6 weeks,
316 the clearance of melphalan decreased from 8.1 mL/min/kg after the first course, to 5.5 mL/min/kg after the third
317 course, but did not decrease appreciably after the third course. Mean (±SD) peak melphalan plasma
318 concentrations in myeloma patients given IV melphalan at doses of 10 or 20 mg/m² were 1.2 ± 0.4 and 2.8 ± 1.9
319 mcg/mL, respectively.

321 ***Distribution***

322 The steady-state volume of distribution of melphalan is 0.5 L/kg. Melphalan penetrates into cerebrospinal fluid
323 (CSF). Average melphalan binding to plasma proteins ranges from approximately 50% to 90%. Serum albumin
324 is the major binding protein, accounting for approximately 40% to 60% of the plasma protein binding, while α1-
325 acid glycoprotein accounts for about 20% of the plasma protein binding. Approximately 30% of melphalan is
326 (covalently) irreversibly bound to plasma proteins.

328 ***Elimination***

329 Metabolism

330 Melphalan is eliminated from plasma primarily by chemical hydrolysis to inactive monohydroxymelphalan and
331 dihydroxymelphalan.

333 Excretion

334 The contribution of renal excretion to melphalan clearance appears to be low (mean values of amount of
335 melphalan excreted in urine range from 5.8-21.3%).

337 ***Specific Populations***

338 Patient Body Weight

339 A typical patient with an ideal body weight (IBW) of 45 kg has a 28% decrease in clearance relative to a patient
340 with IBW of 70 kg, while a patient with an IBW of 100 kg has a 31% increase in clearance as compared to a
341 patient with an IBW of 70 kg.

343 Renal Impairment

344 A decrease in estimated creatinine CL from 100 mL/min to 30 mL/min results in 28.2% reduction in CL for a
345 typical person with an IBW of 70 kg.

347 **13 NONCLINICAL TOXICOLOGY**

348 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

349 Adequate and well-controlled carcinogenicity studies have not been conducted in animals. However,
350 intraperitoneal (IP) administration of melphalan in rats (5.4 to 10.8 mg/m²) and in mice (2.25 to 4.5 mg/m²) 3
351 times per week for 6 months followed by 12 months post-dose observation produced peritoneal sarcomas and
352 lung tumors, respectively.

354 Intramuscular administration of melphalan at 6 and 60 mg/m² produced structural aberrations of the chromatid
355 and chromosomes in bone marrow cells of Wistar rats.

357 14 CLINICAL STUDIES

358 14.1 Myeloablative Conditioning in Patients with Multiple Myeloma Undergoing ASCT

359 An open-label, single-arm, non-randomized trial of Evomela was conducted at 5 US centers. The 61 patients
360 enrolled had symptomatic multiple myeloma, and had at least 2×10^6 CD34+ cells/kg cryopreserved stem cells
361 available. The median age was 62 years (range 32 to 73); 57% male, 80% white, 18% black, 2% Asian.
362 Evomela was administered at 100 mg/m²/day over 30 minutes by IV infusion for two consecutive days (Day -3
363 and Day -2) prior to ASCT (Day 0).

364
365 The objective of the trial was to determine the overall safety and toxicity profile of 200 mg/m² of Evomela in
366 patients with multiple myeloma undergoing ASCT. [See Adverse Reactions (6.1)] The efficacy was evaluated
367 by the International Myeloma Working Group response criteria comparing the disease response immediately
368 prior to the ASCT procedure to the disease response assessed 90 to 100 days post-transplant. In addition,
369 successful myeloablation, and time to engraftment were evaluated.

370
371 The overall response rate (partial response or better) improved from 79% (48 of 61) prior to the ASCT
372 procedure to 95% (58 of 61) at 90 to 100 days post-transplant. There was also an increase in the number of
373 patients with a stringent complete response from 0 patients prior to the ASCT procedure to 16% (10 of 61) at 90
374 to 100 days post-transplant.

375
376 Myeloablation and engraftment were evaluated by complete blood cell count tests daily until neutrophil and
377 platelet engraftment, and then weekly until Day 30, and at Day 60 and Day 90-100. Myeloablation was defined
378 as any of the following: absolute neutrophil count (ANC) < 500/mm³, absolute lymphocyte count < 100/mm³,
379 or platelet count < 20,000/mm³. Neutrophil engraftment was defined as ANC > 500/mm³ ×3 consecutive daily
380 assessments. Platelet engraftment was defined as untransfused platelet counts > 20,000/mm³ ×3 consecutive
381 daily assessments. Nonengraftment was defined as failure to reach an ANC > 500/mm³ ×3 consecutive daily
382 assessments by Day 90-100.

383
384 Myeloablation, neutrophil engraftment and platelet engraftment were achieved by all 61 patients. Myeloablation
385 occurred on ASCT Day 5 (range ASCT days -1 to 6) with the median time to myeloablation from dosing of 8
386 days. The median time to neutrophil engraftment was 12 days (range ASCT days 10 to 16). The median time to
387 platelet engraftment was 13 days (range ASCT days 10 to 28).

388 389 14.2 Palliative Treatment of Patients with Multiple Myeloma

390 A randomized trial compared prednisone plus IV melphalan to prednisone plus oral melphalan in the treatment
391 of multiple myeloma. As discussed below, Overall Response Rates at Week 22 were comparable; however,
392 because of changes in trial design, conclusions as to the relative activity of the 2 formulations after Week 22 are
393 impossible to make.

394
395 Both arms received oral prednisone starting at 0.8 mg/kg/day with doses tapered over 6 weeks. Melphalan doses
396 in each arm were:

397 **Arm 1:** Oral melphalan 0.15 mg/kg/day x 7 followed by 0.05 mg/kg/day when WBC began to rise.

398 **Arm 2:** IV melphalan 16 mg/m² q 2 weeks x 4 (over 6 weeks) followed by the same dose every 4 weeks.

399
400 One hundred seven patients were randomized to the oral melphalan arm and 203 patients to the IV melphalan
401 arm. More patients had a poor-risk classification (58% versus 44%) and high tumor load (51% versus 34%) on
402 the oral arm compared to the IV arm (P<0.04). Response rates at Week 22 are shown in the following table:

403
404 **Table 2: Response Rates at Week 22 for Patients with Multiple Myeloma Who Received Oral or IV**
405 **Melphalan with Prednisone**

Initial Arm	Evaluable Patients	Responders n (%)	P
Oral melphalan	100	44 (44%)	P>0.2
IV melphalan	195	74 (38%)	

407

408 Because of changes in protocol design after Week 22, other efficacy parameters such as Response Duration and
409 Survival could not be compared.

410

411 **15 REFERENCES**

412 1 OSHA Hazardous Drugs. OSHA. [Accessed on 9 December 2014, from
413 <http://www.osha.gov/SLTC/hazardousdrugs/index.html>].

414

415 **16 HOW SUPPLIED/STORAGE AND HANDLING**416 **16.1 How Supplied**

417

418 Evomela is supplied in a single carton containing one (1) vial. Each 50 mg vial contains a white to off-white
419 lyophilized powder in single-dose vial for reconstitution (after reconstitution the solution is clear and colorless
420 to light yellow). Each vial contains 50 mg melphalan free base equivalent to 56 mg melphalan hydrochloride.

421

422 NDC 68152-109-00: Individual carton of Evomela 20 mL single-dose vial containing 50 mg melphalan free
423 base.

424

425 **16.2 Storage and Handling**

426 Store Evomela at room temperature 25°C (77°F). Temperature excursions are permitted between 15-30°C (59-
427 86°F). [see USP Controlled Room Temperature]

428

429 Evomela is light sensitive. Retain in original carton until use.

430

431 Melphalan is a cytotoxic drug. Follow special handling and disposal procedures [see *References (15)*].

432

433 **17 PATIENT COUNSELING INFORMATION**

434 Advise the patient to read the FDA-approved patient labeling (Patient Information).

435

436 Advise patients or their caregivers of the following:

437

438 Low Blood Cell Counts

- 439 • To report any signs or symptoms of thrombocytopenia, leukopenia (neutropenia and lymphopenia), and
440 anemia. Inform patients of the need for routine blood counts [see *Warnings and Precautions (5.1)*].

441

442 Mucositis

- 443 • Inform patients of the signs and symptoms of mucositis. Instruct patients on ways to reduce the risk of its
444 development, and on ways to maintain nutrition and control discomfort if it occurs [see *Warnings and*
445 *Precautions (5.2)*].

446

447 Nausea, Vomiting and Diarrhea

- 448 • To report symptoms of nausea, vomiting and diarrhea, so that appropriate antiemetic and/or antidiarrheal
449 medications can be administered [see *Warnings and Precautions (5.2)*].

450

451 Allergic Reactions

- 452 • To immediately report symptoms of hypersensitivity reactions including changes involving the skin,
453 breathing or heart rate, so that antihistamine or corticosteroid therapy can be administered [*see Warnings*
454 *and Precautions (5.4)*].

455

456 Secondary cancers

- 457 • To understand the potential long-term risks related to secondary malignancy [*see Warnings and Precautions*
458 *(5.5)*].

459

460 Birth Defects

- 461 • Advise pregnant women of the potential risk to a fetus [*see Warnings and Precautions (5.6) and Use in*
462 *Specific Populations (8.1)*].
- 463 • Advise females of reproductive potential to avoid pregnancy, which may include use of effective
464 contraception during and after treatment with Evomela. Advise females to contact their healthcare provider
465 if they become pregnant, or if pregnancy is suspected, while taking Evomela [*see Warnings and*
466 *Precautions (5.6) and Use in Specific Populations (8.1, 8.3)*].
- 467 • Inform both females and males of reproductive potential about the risk for infertility [*see Warnings and*
468 *Precautions (5.7) and Use in Specific Populations (8.3)*].
- 469 • Advise women that breastfeeding is not recommended during treatment with Evomela [*see Use in Specific*
470 *Populations (8.2)*].
- 471 • Advise males with female sexual partners of reproductive potential that they should use effective
472 contraception during and after treatment with Evomela [*see Use in Specific Populations (8.3)*].

473

474 Manufactured for:

475 Spectrum Pharmaceuticals, Inc.

476 Irvine, CA 92618

477

PATIENT INFORMATION
EVOMELA (ev-ō-meh-lah)
(melphalan) for injection, for intravenous use

What is Evomela?

Evomela is a prescription medicine used in people with a type of cancer called multiple myeloma:

- before receiving a stem cell transplant (conditioning treatment)
- as a part of care to support symptom relief (palliative treatment), in people who cannot take medicine by mouth

It is not known if Evomela is safe and effective in children.

Do not receive Evomela if you are allergic to melphalan or any of the ingredients in Evomela. See the end of this leaflet for a complete list of ingredients in Evomela.

Before you receive Evomela, tell your doctor about all of your medical conditions, including if you:

- have an infection
- have had chemotherapy treatment
- have nausea, vomiting, or diarrhea
- have liver or kidney problems
- are pregnant or plan to become pregnant. Evomela can harm your unborn baby. You should not become pregnant during and after treatment with Evomela. Tell your doctor right away if you become pregnant during treatment with Evomela.
 - **Females** who are able to become pregnant should use effective birth control during and after treatment with Evomela. Talk with your doctor about how long to use birth control after treatment with Evomela.
 - **Males** who have female partners who are able to become pregnant should use effective birth control during and after treatment with Evomela. Talk with your doctor about how long to use birth control after treatment with Evomela.
- are breastfeeding or plan to breastfeed. It is not known if Evomela passes into your breast milk. You should not breastfeed during treatment with Evomela.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive Evomela?

- Evomela is given to you into your vein through an intravenous (IV) line over 15 to 30 minutes.
- Your doctor will do blood tests before and during your treatment with Evomela.
- Your doctor may prescribe medicines to help prevent nausea.

What are the possible side effects of Evomela?

Evomela may cause serious side effects, including:

- **Low blood cell counts** are common with Evomela and can be serious. Your doctor will do blood tests as needed to check your blood counts during your treatment with Evomela.
 - **Low platelet counts:** Tell your doctor right away if you have unusual bleeding or bruising under your skin.
 - **Low red blood cell counts:** Tell your doctor if you are feeling weak, tired, or you get tired easily, you look pale, or you feel short of breath.
 - **Low white blood cell counts:** A low white blood cell count can cause you to get infections, which may be serious. Tell your doctor right away if you have symptoms of infection, such as fever, chills, cough, pain, or burning during urination.
- **Redness and sores of the lining of the mouth, lips, throat, stomach, and genitals (mucositis).** Discomfort or pain due to mucositis may happen during treatment with Evomela. Your doctor will tell you about ways to maintain nutrition and help control the discomfort from mucositis.
- **Nausea, vomiting, and diarrhea** are common with Evomela and can sometimes be serious. Tell your doctor if you get nausea, vomiting, or diarrhea. Your doctor may prescribe medicines to help prevent or treat these side effects.
- **Liver problems.** Your doctor will check you for liver problems during treatment with Evomela. Tell your doctor right away if you get any of the following signs or symptoms:
 - yellowing of your skin or the whites of your eyes
 - pain on the right side of your stomach-area (abdomen)
 - severe nausea or vomiting
 - dark urine (tea colored)
- **Allergic reactions.** Tell your doctor right away if you get any of the following signs or symptoms:
 - skin reactions, including welts, rash, itching, and redness
 - fast heartbeat
 - shortness of breath or trouble breathing
 - feel lightheaded or dizzy
 - blurry vision
 - swelling of your face, tongue, or throat
- **Secondary cancers.** New cancers have happened in people who have been treated with Evomela.
- **Infertility.** Evomela may cause fertility problems in males and females. Talk to your doctor if this is a concern for you.

The most common side effects of Evomela include tiredness and low potassium level.

These are not all the possible side effects of Evomela. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Evomela.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Evomela for a condition for which it was not prescribed. Do not give Evomela to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about Evomela that is written for health professionals.

What are the ingredients in Evomela?

Active ingredient: melphalan hydrochloride

Inactive ingredient: Betadex Sulfobutyl Ether Sodium

Manufactured for: Spectrum Pharmaceuticals, Inc. Irvine, CA 92618

For more information, go to www.evomela.com or call 1-888-292-9617.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Issued: March 2016