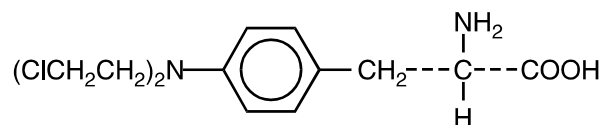


ALKERAN[®]**(melphalan hydrochloride)****for Injection****WARNING**

Melphalan should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Severe bone marrow suppression with resulting infection or bleeding may occur. Controlled trials comparing intravenous (IV) to oral melphalan have shown more myelosuppression with the IV formulation. Hypersensitivity reactions, including anaphylaxis, have occurred in approximately 2% of patients who received the IV formulation. Melphalan is leukemogenic in humans. Melphalan produces chromosomal aberrations in vitro and in vivo and, therefore, should be considered potentially mutagenic in humans.

DESCRIPTION

Melphalan, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcolysin, is a phenylalanine derivative of nitrogen mustard. Melphalan is a bifunctional alkylating agent that is active against selected human neoplastic diseases. It is known chemically as 4-[bis(2-chloroethyl)amino]-L-phenylalanine. The molecular formula is $C_{13}H_{18}Cl_2N_2O_2$ and the molecular weight is 305.20. The structural formula is:



Melphalan is the active L-isomer of the compound and was first synthesized in 1953 by Bergel and Stock; the D-isomer, known as medphalan, is less active against certain animal tumors, and the dose needed to produce effects on chromosomes is larger than that required with the L-isomer. The racemic (DL-) form is known as merphalan or sarcolysin.

Melphalan is practically insoluble in water and has a pK_{a1} of ~ 2.5 .

29 ALKERAN for Injection is supplied as a sterile, nonpyrogenic, freeze-dried powder. Each
30 single-use vial contains melphalan hydrochloride equivalent to 50 mg melphalan and 20 mg
31 povidone. ALKERAN for Injection is reconstituted using the sterile diluent provided. Each vial of
32 sterile diluent contains sodium citrate 0.2 g, propylene glycol 6.0 mL, ethanol (96%) 0.52 mL, and
33 Water for Injection to a total of 10 mL. ALKERAN for Injection is administered intravenously.

34

35 **CLINICAL PHARMACOLOGY**

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

40 **Pharmacokinetics:** The pharmacokinetics of melphalan after IV administration has been
41 extensively studied in adult patients. Following injection, drug plasma concentrations declined
42 rapidly in a biexponential manner with distribution phase and terminal elimination phase half-lives
43 of approximately 10 and 75 minutes, respectively. Estimates of average total body clearance varied
44 among studies, but typical values of approximately 7 to 9 mL/min/kg (250 to 325 mL/min/m²) were
45 observed. One study has reported that on repeat dosing of 0.5 mg/kg every 6 weeks, the clearance of
46 melphalan decreased from 8.1 mL/min/kg after the first course, to 5.5 mL/min/kg after the third
47 course, but did not decrease appreciably after the third course. Mean (\pm SD) peak melphalan plasma
48 concentrations in myeloma patients given IV melphalan at doses of 10 or 20 mg/m² were 1.2 ± 0.4
49 and 2.8 ± 1.9 mcg/mL, respectively.

50 The steady-state volume of distribution of melphalan is 0.5 L/kg. Penetration into cerebrospinal
51 fluid (CSF) is low. The extent of melphalan binding to plasma proteins ranges from 60% to 90%.
52 Serum albumin is the major binding protein, while α_1 -acid glycoprotein appears to account for
53 about 20% of the plasma protein binding. Approximately 30% of the drug is (covalently)
54 irreversibly bound to plasma proteins. Interactions with immunoglobulins have been found to be
55 negligible.

56 Melphalan is eliminated from plasma primarily by chemical hydrolysis to
57 monohydroxymelphalan and dihydroxymelphalan. Aside from these hydrolysis products, no other
58 melphalan metabolites have been observed in humans. Although the contribution of renal

59 elimination to melphalan clearance appears to be low, one study noted an increase in the occurrence
60 of severe leukopenia in patients with elevated BUN after 10 weeks of therapy.

61 **Clinical Trial:** A randomized trial compared prednisone plus IV melphalan to prednisone plus oral
62 melphalan in the treatment of myeloma. As discussed below, overall response rates at week 22 were
63 comparable; however, because of changes in trial design, conclusions as to the relative activity of
64 the 2 formulations after week 22 are impossible to make.

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

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

68 Arm 2 IV melphalan 16 mg/m² q 2 weeks x 4 (over 6 weeks) followed by the same dose every
69 4 weeks.

70 Doses of melphalan were adjusted according to the following criteria:

71

72 **Table 1. Criteria for Dosage Adjustment in a Randomized Clinical Trial**

WBC/mm ³	Platelets	Percent of Full Dose
≥4,000	≥100,000	100
≥3,000	≥75,000	75
≥2,000	≥50,000	50
≥2,000	<50,000	0

73

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

78

79 **Table 2. Response Rates at Week 22**

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

80
81 Because of changes in protocol design after week 22, other efficacy parameters such as response
82 duration and survival cannot be compared.

83 Severe myelotoxicity (WBC \leq 1,000 and/or platelets \leq 25,000) was more common in the IV
84 melphalan arm (28%) than in the oral melphalan arm (11%).

85 An association was noted between poor renal function and myelosuppression; consequently, an
86 amendment to the protocol required a 50% reduction in IV melphalan dose if the BUN was
87 \geq 30 mg/dL. The rate of severe leukopenia in the IV arm in the patients with BUN over 30 mg/dL
88 decreased from 50% (8/16) before protocol amendment to 11% (3/28) (*P* = 0.01) after the
89 amendment.

90 Before the dosing amendment, there was a 10% (8/77) incidence of drug-related death in the IV
91 arm. After the dosing amendment, this incidence was 3% (3/108). This compares to an overall 1%
92 (1/100) incidence of drug-related death in the oral arm.

93

94 **INDICATIONS AND USAGE**

95 ALKERAN for Injection is indicated for the palliative treatment of patients with multiple
96 myeloma for whom oral therapy is not appropriate.

97

98 **CONTRAINDICATIONS**

99 Melphalan should not be used in patients whose disease has demonstrated prior resistance to this
100 agent. Patients who have demonstrated hypersensitivity to melphalan should not be given the drug.

101

102 **WARNINGS**

103 **Melphalan should be administered in carefully adjusted dosage by or under the supervision**
104 **of experienced physicians who are familiar with the drug's actions and the possible**
105 **complications of its use.**

106 As with other nitrogen mustard drugs, excessive dosage will produce marked bone marrow
107 suppression. Bone marrow suppression is the most significant toxicity associated with ALKERAN
108 for Injection in most patients. Therefore, the following tests should be performed at the start of
109 therapy and prior to each subsequent dose of ALKERAN: platelet count, hemoglobin, white blood
110 cell count, and differential. Thrombocytopenia and/or leukopenia are indications to withhold further
111 therapy until the blood counts have sufficiently recovered. Frequent blood counts are essential to
112 determine optimal dosage and to avoid toxicity. Dose adjustment on the basis of blood counts at the
113 nadir and day of treatment should be considered.

114 Hypersensitivity reactions including anaphylaxis have occurred in approximately 2% of patients
115 who received the IV formulation (see ADVERSE REACTIONS). These reactions usually occur
116 after multiple courses of treatment. Treatment is symptomatic. The infusion should be terminated
117 immediately, followed by the administration of volume expanders, pressor agents, corticosteroids,
118 or antihistamines at the discretion of the physician. If a hypersensitivity reaction occurs, IV or oral
119 melphalan should not be readministered since hypersensitivity reactions have also been reported
120 with oral melphalan.

121 **Carcinogenesis:** Secondary malignancies, including acute nonlymphocytic leukemia,
122 myeloproliferative syndrome, and carcinoma, have been reported in patients with cancer treated
123 with alkylating agents (including melphalan). Some patients also received other chemotherapeutic
124 agents or radiation therapy. Precise quantitation of the risk of acute leukemia, myeloproliferative
125 syndrome, or carcinoma is not possible. Published reports of leukemia in patients who have
126 received melphalan (and other alkylating agents) suggest that the risk of leukemogenesis increases
127 with chronicity of treatment and with cumulative dose. In one study, the 10-year cumulative risk of
128 developing acute leukemia or myeloproliferative syndrome after oral melphalan therapy was 19.5%
129 for cumulative doses ranging from 730 to 9,652 mg. In this same study, as well as in an additional
130 study, the 10-year cumulative risk of developing acute leukemia or myeloproliferative syndrome
131 after oral melphalan therapy was less than 2% for cumulative doses under 600 mg. This does not
132 mean that there is a cumulative dose below which there is no risk of the induction of secondary

133 malignancy. The potential benefits from melphalan therapy must be weighed on an individual basis
134 against the possible risk of the induction of a second malignancy.

135 Adequate and well-controlled carcinogenicity studies have not been conducted in animals.

136 However, intraperitoneal (IP) administration of melphalan in rats (5.4 to 10.8 mg/m²) and in mice
137 (2.25 to 4.5 mg/m²) 3 times per week for 6 months followed by 12 months post-dose observation
138 produced peritoneal sarcoma and lung tumors, respectively.

139 **Mutagenesis:** Melphalan has been shown to cause chromatid or chromosome damage in humans.
140 Intramuscular administration of melphalan at 6 and 60 mg/m² produced structural aberrations of the
141 chromatid and chromosomes in bone marrow cells of Wistar rats.

142 **Impairment of Fertility:** Melphalan causes suppression of ovarian function in premenopausal
143 women, resulting in amenorrhea in a significant number of patients. Reversible and irreversible
144 testicular suppression have also been reported.

145 **Pregnancy:** Pregnancy Category D. Melphalan may cause fetal harm when administered to a
146 pregnant woman. While adequate animal studies have not been conducted with IV melphalan, oral
147 (6 to 18 mg/m²/day for 10 days) and IP (18 mg/m²) administration in rats was embryolethal and
148 teratogenic. Malformations resulting from melphalan included alterations of the brain
149 (underdevelopment, deformation, meningocele, and encephalocele) and eye (anophthalmia and
150 microphthalmos), reduction of the mandible and tail, as well as hepatocoele (exomphaly). There are
151 no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy,
152 or if the patient becomes pregnant while taking this drug, the patient should be apprised of the
153 potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming
154 pregnant.

155

156 **PRECAUTIONS**

157 **General:** In all instances where the use of ALKERAN for Injection is considered for
158 chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of
159 adverse events. Melphalan should be used with extreme caution in patients whose bone marrow
160 reserve may have been compromised by prior irradiation or chemotherapy or whose marrow
161 function is recovering from previous cytotoxic therapy.

162 Dose reduction should be considered in patients with renal insufficiency receiving IV melphalan.
163 In one trial, increased bone marrow suppression was observed in patients with BUN levels

164 ≥ 30 mg/dL. A 50% reduction in the IV melphalan dose decreased the incidence of severe bone
165 marrow suppression in the latter portion of this study.

166 **Information for Patients:** Patients should be informed that the major acute toxicities of
167 melphalan are related to bone marrow suppression, hypersensitivity reactions, gastrointestinal
168 toxicity, and pulmonary toxicity. The major long-term toxicities are related to infertility and
169 secondary malignancies. Patients should never be allowed to take the drug without close medical
170 supervision and should be advised to consult their physicians if they experience skin rash, signs or
171 symptoms of vasculitis, bleeding, fever, persistent cough, nausea, vomiting, amenorrhea, weight
172 loss, or unusual lumps/masses. Women of childbearing potential should be advised to avoid
173 becoming pregnant.

174 **Laboratory Tests:** Periodic complete blood counts with differentials should be performed during
175 the course of treatment with melphalan. At least 1 determination should be obtained prior to each
176 dose. Patients should be observed closely for consequences of bone marrow suppression, which
177 include severe infections, bleeding, and symptomatic anemia (see WARNINGS).

178 **Drug Interactions:** The development of severe renal failure has been reported in patients treated
179 with a single dose of IV melphalan followed by standard oral doses of cyclosporine. Cisplatin may
180 affect melphalan kinetics by inducing renal dysfunction and subsequently altering melphalan
181 clearance. IV melphalan may also reduce the threshold for BCNU lung toxicity. When nalidixic
182 acid and IV melphalan are given simultaneously, the incidence of severe hemorrhagic necrotic
183 enterocolitis has been reported to increase in pediatric patients.

184 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** See WARNINGS section.

185 **Pregnancy: Teratogenic Effects:** Pregnancy Category D: See WARNINGS section.

186 **Nursing Mothers:** It is not known whether this drug is excreted in human milk. IV melphalan
187 should not be given to nursing mothers.

188 **Pediatric Use:** The safety and effectiveness in pediatric patients have not been established.

189 **Geriatric Use:** Clinical studies of ALKERAN for Injection did not include sufficient numbers of
190 subjects aged 65 and over to determine whether they respond differently from younger subjects.
191 Other reported clinical experience has not identified differences in responses between the elderly
192 and younger patients. In general, dose selection for an elderly patient should be cautious, usually
193 starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic,
194 renal, or cardiac function, and of concomitant disease or other drug therapy.

195

196 **ADVERSE REACTIONS (see OVERDOSAGE)**

197 The following information on adverse reactions is based on data from both oral and IV
198 administration of melphalan as a single agent, using several different dose schedules for treatment
199 of a wide variety of malignancies.

200 **Hematologic:** The most common side effect is bone marrow suppression. White blood cell count
201 and platelet count nadirs usually occur 2 to 3 weeks after treatment, with recovery in 4 to 5 weeks
202 after treatment. Irreversible bone marrow failure has been reported.

203 **Gastrointestinal:** Gastrointestinal disturbances such as nausea and vomiting, diarrhea, and oral
204 ulceration occur infrequently. Hepatic disorders ranging from abnormal liver function tests to
205 clinical manifestations such as hepatitis and jaundice have been reported. Hepatic veno-occlusive
206 disease has been reported.

207 **Hypersensitivity:** Acute hypersensitivity reactions including anaphylaxis were reported in 2.4%
208 of 425 patients receiving ALKERAN for Injection for myeloma (see WARNINGS). These reactions
209 were characterized by urticaria, pruritus, edema, and in some patients, tachycardia, bronchospasm,
210 dyspnea, and hypotension. These patients appeared to respond to antihistamine and corticosteroid
211 therapy. If a hypersensitivity reaction occurs, IV or oral melphalan should not be readministered
212 since hypersensitivity reactions have also been reported with oral melphalan.

213 **Miscellaneous:** Other reported adverse reactions include skin hypersensitivity, skin ulceration at
214 injection site, skin necrosis rarely requiring skin grafting, vasculitis, alopecia, hemolytic anemia,
215 allergic reaction, pulmonary fibrosis, and interstitial pneumonitis.

216

217 **OVERDOSAGE**

218 Overdoses resulting in death have been reported. Overdoses, including doses up to 290 mg/m²,
219 have produced the following symptoms: severe nausea and vomiting, decreased consciousness,
220 convulsions, muscular paralysis, and cholinomimetic effects. Severe mucositis, stomatitis, colitis,
221 diarrhea, and hemorrhage of the gastrointestinal tract occur at high doses (>100 mg/m²). Elevations
222 in liver enzymes and veno-occlusive disease occur infrequently. Significant hyponatremia caused
223 by an associated inappropriate secretion of ADH syndrome has been observed. Nephrotoxicity and
224 adult respiratory distress syndrome have been reported rarely. The principal toxic effect is bone
225 marrow suppression. Hematologic parameters should be closely followed for 3 to 6 weeks. An

226 uncontrolled study suggests that administration of autologous bone marrow or hematopoietic
227 growth factors (i.e., sargramostim, filgrastim) may shorten the period of pancytopenia. General
228 supportive measures together with appropriate blood transfusions and antibiotics should be
229 instituted as deemed necessary by the physician. This drug is not removed from plasma to any
230 significant degree by hemodialysis or hemoperfusion. A pediatric patient survived a 254-mg/m²
231 overdose treated with standard supportive care.

232

233 **DOSAGE AND ADMINISTRATION**

234 The usual IV dose is 16 mg/m². Dosage reduction of up to 50% should be considered in patients
235 with renal insufficiency (BUN ≥30 mg/dL) (see PRECAUTIONS: General). The drug is
236 administered as a single infusion over 15 to 20 minutes. Melphalan is administered at 2-week
237 intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals. Available
238 evidence suggests about one third to one half of the patients with multiple myeloma show a
239 favorable response to the drug. Experience with oral melphalan suggests that repeated courses
240 should be given since improvement may continue slowly over many months, and the maximum
241 benefit may be missed if treatment is abandoned prematurely. Dose adjustment on the basis of
242 blood cell counts at the nadir and day of treatment should be considered.

243 **Administration Precautions:** As with other toxic compounds, caution should be exercised in
244 handling and preparing the solution of ALKERAN. Skin reactions associated with accidental
245 exposure may occur. The use of gloves is recommended. If the solution of ALKERAN contacts the
246 skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

247 Procedures for proper handling and disposal of anticancer drugs should be considered. Several
248 guidelines on this subject have been published.¹⁻⁷ There is no general agreement that all of the
249 procedures recommended in the guidelines are necessary or appropriate.

250 Parenteral drug products should be visually inspected for particulate matter and discoloration
251 prior to administration whenever solution and container permit. If either occurs, do not use this
252 product.

253 **Preparation for Administration/Stability**

254 1. ALKERAN for Injection must be reconstituted by rapidly injecting 10 mL of the supplied
255 diluent directly into the vial of lyophilized powder using a sterile needle (20-gauge or larger
256 needle diameter) and syringe. Immediately shake vial vigorously until a clear solution is

257 obtained. This provides a 5-mg/mL solution of melphalan. Rapid addition of the diluent
258 followed by immediate vigorous shaking is important for proper dissolution.

259 2. **Immediately** dilute the dose to be administered in 0.9% Sodium Chloride Injection, USP, to a
260 concentration not greater than 0.45 mg/mL.

261 3. Administer the diluted product over a minimum of 15 minutes.

262 4. Complete administration within 60 minutes of reconstitution.

263 **The time between reconstitution/dilution and administration of ALKERAN should be kept**
264 **to a minimum because reconstituted and diluted solutions of ALKERAN are unstable.** Over as
265 short a time as 30 minutes, a citrate derivative of melphalan has been detected in reconstituted
266 material from the reaction of ALKERAN with Sterile Diluent for ALKERAN. Upon further dilution
267 with saline, nearly 1% label strength of melphalan hydrolyzes every 10 minutes.

268 A precipitate forms if the reconstituted solution is stored at 5°C. **DO NOT REFRIGERATE THE**
269 **RECONSTITUTED PRODUCT.**

270

271 **HOW SUPPLIED**

272 ALKERAN for Injection is supplied in a carton containing one single-use clear glass vial of
273 freeze-dried melphalan hydrochloride equivalent to 50 mg melphalan and one 10-mL clear glass
274 vial of sterile diluent (NDC 0173-0130-93).

275 **Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light.**

276

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