

1 **PRESCRIBING INFORMATION**

2 **ALKERAN[®]**

3 **(melphalan)**

4 **Tablets**

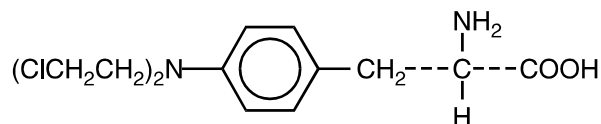
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6 **WARNING**

7 ALKERAN (melphalan) should be administered under the supervision of a qualified
8 physician experienced in the use of cancer chemotherapeutic agents. Severe bone marrow
9 suppression with resulting infection or bleeding may occur. Melphalan is leukemogenic in
10 humans.

11 Melphalan produces chromosomal aberrations in vitro and in vivo and, therefore, should be
12 considered potentially mutagenic in humans.

13
14 **DESCRIPTION**

15 ALKERAN (melphalan), also known as L-phenylalanine mustard, phenylalanine mustard,
16 L-PAM, or L-sarcolysin, is a phenylalanine derivative of nitrogen mustard. Melphalan is a
17 bifunctional alkylating agent which is active against selective human neoplastic diseases. It is
18 known chemically as 4-[bis(2-chloroethyl)amino]-L-phenylalanine. The molecular formula is
19 C₁₃H₁₈Cl₂N₂O₂ and the molecular weight is 305.20. The structural formula is:



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

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

28 ALKERAN (melphalan) is available in tablet form for oral administration. Each film-coated
29 tablet contains 2 mg melphalan and the inactive ingredients colloidal silicon dioxide,
30 crospovidone, hypromellose, macrogol/PEG 400, magnesium stearate, microcrystalline cellulose,
31 and titanium dioxide.

32

33 **CLINICAL PHARMACOLOGY**

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

38 **Pharmacokinetics:** The pharmacokinetics of ALKERAN after oral administration has been
39 extensively studied in adult patients. Plasma melphalan levels are highly variable after oral
40 dosing, both with respect to the time of the first appearance of melphalan in plasma (range
41 approximately 0 to 6 hours) and to the peak plasma concentration (C_{max}) (range 70 to
42 4,000 ng/mL, depending upon the dose) achieved. These results may be due to incomplete
43 intestinal absorption, a variable “first pass” hepatic metabolism, or to rapid hydrolysis. Five
44 patients were studied after both oral and intravenous (IV) dosing with 0.6 mg/kg as a single
45 bolus dose by each route. The areas under the plasma concentration-time curves (AUC) after oral
46 administration averaged $61\% \pm 26\%$ (\pm standard deviation [SD]; range 25% to 89%) of those
47 following IV administration. In 18 patients given a single oral dose of 0.6 mg/kg of ALKERAN,
48 the terminal elimination plasma half-life ($t_{1/2}$) of parent drug was 1.5 ± 0.83 hours. The 24-hour
49 urinary excretion of parent drug in these patients was $10\% \pm 4.5\%$, suggesting that renal
50 clearance is not a major route of elimination of parent drug. In a separate study in 18 patients
51 given single oral doses of 0.2 to 0.25 mg/kg of ALKERAN, C_{max} and AUC, when dose adjusted
52 to a dose of 14 mg, were (mean \pm SD) 212 ± 74 ng/mL and 498 ± 137 ng•hr/mL, respectively.
53 Elimination phase $t_{1/2}$ in these patients was approximately 1 hour and the median t_{max} was 1 hour.

54 One study using universally labeled ¹⁴C-melphalan, found substantially less radioactivity in
55 the urine of patients given the drug by mouth (30% of administered dose in 9 days) than in the
56 urine of those given it intravenously (35% to 65% in 7 days). Following either oral or IV
57 administration, the pattern of label recovery was similar, with the majority being recovered in the
58 first 24 hours. Following oral administration, peak radioactivity occurred in plasma at 2 hours

59 and then disappeared with a half-life of approximately 160 hours. In 1 patient where parent drug
60 (rather than just radiolabel) was determined, the melphalan half-disappearance time was
61 67 minutes.

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

68 Melphalan is eliminated from plasma primarily by chemical hydrolysis to
69 monohydroxymelphalan and dihydroxymelphalan. Aside from these hydrolysis products, no
70 other melphalan metabolites have been observed in humans. Although the contribution of renal
71 elimination to melphalan clearance appears to be low, one pharmacokinetic study showed a
72 significant positive correlation between the elimination rate constant for melphalan and renal
73 function and a significant negative correlation between renal function and the area under the
74 plasma melphalan concentration/time curve.

75

76 **INDICATIONS AND USAGE**

77 ALKERAN Tablets are indicated for the palliative treatment of multiple myeloma and for the
78 palliation of non-resectable epithelial carcinoma of the ovary.

79

80 **CONTRAINDICATIONS**

81 ALKERAN should not be used in patients whose disease has demonstrated a prior resistance
82 to this agent. Patients who have demonstrated hypersensitivity to melphalan should not be given
83 the drug.

84

85 **WARNINGS**

86 **ALKERAN should be administered in carefully adjusted dosage by or under the**
87 **supervision of experienced physicians who are familiar with the drug's actions and the**
88 **possible complications of its use.**

89 As with other nitrogen mustard drugs, excessive dosage will produce marked bone marrow
90 suppression. Bone marrow suppression is the most significant toxicity associated with
91 ALKERAN in most patients. Therefore, the following tests should be performed at the start of
92 therapy and prior to each subsequent course of ALKERAN: platelet count, hemoglobin, white
93 blood cell count, and differential. Thrombocytopenia and/or leukopenia are indications to
94 withhold further therapy until the blood counts have sufficiently recovered. Frequent blood
95 counts are essential to determine optimal dosage and to avoid toxicity (see PRECAUTIONS:
96 Laboratory Tests). Dose adjustment on the basis of blood counts at the nadir and day of
97 treatment should be considered.

98 Hypersensitivity reactions, including anaphylaxis, have occurred rarely (see ADVERSE
99 REACTIONS). These reactions have occurred after multiple courses of treatment and have
100 recurred in patients who experienced a hypersensitivity reaction to IV ALKERAN. If a
101 hypersensitivity reaction occurs, oral or IV ALKERAN should not be readministered.

102 **Carcinogenesis:** Secondary malignancies, including acute nonlymphocytic leukemia,
103 myeloproliferative syndrome, and carcinoma have been reported in patients with cancer treated
104 with alkylating agents (including melphalan). Some patients also received other
105 chemotherapeutic agents or radiation therapy. Precise quantitation of the risk of acute leukemia,
106 myeloproliferative syndrome, or carcinoma is not possible. Published reports of leukemia in
107 patients who have received melphalan (and other alkylating agents) suggest that the risk of
108 leukemogenesis increases with chronicity of treatment and with cumulative dose. In one study,
109 the 10-year cumulative risk of developing acute leukemia or myeloproliferative syndrome after
110 melphalan therapy was 19.5% for cumulative doses ranging from 730 mg to 9,652 mg. In this
111 same study, as well as in an additional study, the 10-year cumulative risk of developing acute
112 leukemia or myeloproliferative syndrome after melphalan therapy was less than 2% for
113 cumulative doses under 600 mg. This does not mean that there is a cumulative dose below which
114 there is no risk of the induction of secondary malignancy. The potential benefits from melphalan
115 therapy must be weighed on an individual basis against the possible risk of the induction of a
116 second malignancy.

117 Adequate and well-controlled carcinogenicity studies have not been conducted in animals.
118 However, i.p. administration of melphalan in rats (5.4 to 10.8 mg/m²) and in mice (2.25 to

119 4.5 mg/m²) 3 times per week for 6 months followed by 12 months post-dose observation
120 produced peritoneal sarcoma and lung tumors, respectively.

121 **Mutagenesis:** ALKERAN has been shown to cause chromatid or chromosome damage in
122 humans. Intramuscular administration of ALKERAN at 6 and 60 mg/m² produced structural
123 aberrations of the chromatid and chromosomes in bone marrow cells of Wistar rats.

124 **Impairment of Fertility:** ALKERAN causes suppression of ovarian function in premenopausal
125 women, resulting in amenorrhea in a significant number of patients. Reversible and irreversible
126 testicular suppression have also been reported.

127 **Pregnancy:** Pregnancy Category D. ALKERAN may cause fetal harm when administered to a
128 pregnant woman. Melphalan was embryo-lethal and teratogenic in rats following oral (6 to
129 18 mg/m²/day for 10 days) and intraperitoneal (18 mg/m²) administration. Malformations
130 resulting from melphalan included alterations of the brain (underdevelopment, deformation,
131 meningocele, and encephalocele) and eye (anophthalmia and microphthalmos), reduction of the
132 mandible and tail, as well as hepatocele (exomphaly).

133 There are no adequate and well-controlled studies in pregnant women. If this drug is used
134 during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be
135 apprised of the potential hazard to the fetus. Women of childbearing potential should be advised
136 to avoid becoming pregnant.

137

138 **PRECAUTIONS**

139 **General:** In all instances where the use of ALKERAN is considered for chemotherapy, the
140 physician must evaluate the need and usefulness of the drug against the risk of adverse events.
141 ALKERAN should be used with extreme caution in patients whose bone marrow reserve may
142 have been compromised by prior irradiation or chemotherapy, or whose marrow function is
143 recovering from previous cytotoxic therapy. If the leukocyte count falls below 3,000 cells/mcL,
144 or the platelet count below 100,000 cells/mcL, ALKERAN should be discontinued until the
145 peripheral blood cell counts have recovered.

146 A recommendation as to whether or not dosage reduction should be made routinely in patients
147 with renal insufficiency cannot be made because:

148 a) There is considerable inherent patient-to-patient variability in the systemic availability of
149 melphalan in patients with normal renal function.

150 b) Only a small amount of the administered dose appears as parent drug in the urine of patients
151 with normal renal function.

152 Patients with azotemia should be closely observed, however, in order to make dosage
153 reductions, if required, at the earliest possible time.

154 **Information for Patients:** Patients should be informed that the major toxicities of ALKERAN
155 are related to bone marrow suppression, hypersensitivity reactions, gastrointestinal toxicity, and
156 pulmonary toxicity. The major long-term toxicities are related to infertility and secondary
157 malignancies. Patients should never be allowed to take the drug without close medical
158 supervision and should be advised to consult their physician if they experience skin rash,
159 vasculitis, bleeding, fever, persistent cough, nausea, vomiting, amenorrhea, weight loss, or
160 unusual lumps/masses. Women of childbearing potential should be advised to avoid becoming
161 pregnant.

162 **Laboratory Tests:** Periodic complete blood counts with differentials should be performed
163 during the course of treatment with ALKERAN. At least one determination should be obtained
164 prior to each treatment course. Patients should be observed closely for consequences of bone
165 marrow suppression, which include severe infections, bleeding, and symptomatic anemia (see
166 WARNINGS).

167 **Drug Interactions:** There are no known drug/drug interactions with oral ALKERAN.

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

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

170 **Nursing Mothers:** It is not known whether this drug is excreted in human milk. ALKERAN
171 should not be given to nursing mothers.

172 **Pediatric Use:** The safety and effectiveness of ALKERAN in pediatric patients have not been
173 established.

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

180

181 **ADVERSE REACTIONS**

182 **Hematologic:** The most common side effect is bone marrow suppression. Although bone
183 marrow suppression frequently occurs, it is usually reversible if melphalan is withdrawn early
184 enough. However, irreversible bone marrow failure has been reported.

185 **Gastrointestinal:** Gastrointestinal disturbances such as nausea and vomiting, diarrhea, and oral
186 ulceration occur infrequently. Hepatic disorders ranging from abnormal liver function tests to
187 clinical manifestations such as hepatitis and jaundice have been reported.

188 **Miscellaneous:** Other reported adverse reactions include: pulmonary fibrosis and interstitial
189 pneumonitis, skin hypersensitivity, vasculitis, alopecia, and hemolytic anemia. Allergic
190 reactions, including rare anaphylaxis, have occurred after multiple courses of treatment.

191

192 **OVERDOSAGE**

193 Overdoses, including doses up to 50 mg/day for 16 days, have been reported. Immediate
194 effects are likely to be vomiting, ulceration of the mouth, diarrhea, and hemorrhage of the
195 gastrointestinal tract. The principal toxic effect is bone marrow suppression. Hematologic
196 parameters should be closely followed for 3 to 6 weeks. An uncontrolled study suggests that
197 administration of autologous bone marrow or hematopoietic growth factors (i.e., sargramostim,
198 filgrastim) may shorten the period of pancytopenia. General supportive measures, together with
199 appropriate blood transfusions and antibiotics, should be instituted as deemed necessary by the
200 physician. This drug is not removed from plasma to any significant degree by hemodialysis.

201

202 **DOSAGE AND ADMINISTRATION**

203 **Multiple Myeloma:** The usual oral dose is 6 mg (3 tablets) daily. The entire daily dose may be
204 given at one time. The dose is adjusted, as required, on the basis of blood counts done at
205 approximately weekly intervals. After 2 to 3 weeks of treatment, the drug should be discontinued
206 for up to 4 weeks, during which time the blood count should be followed carefully. When the
207 white blood cell and platelet counts are rising, a maintenance dose of 2 mg daily may be
208 instituted. Because of the patient-to-patient variation in melphalan plasma levels following oral
209 administration of the drug, several investigators have recommended that the dosage of
210 ALKERAN be cautiously escalated until some myelosuppression is observed in order to assure
211 that potentially therapeutic levels of the drug have been reached.

212 Other dosage regimens have been used by various investigators. Osserman and Takatsuki
213 have used an initial course of 10 mg/day for 7 to 10 days. They report that maximal suppression
214 of the leukocyte and platelet counts occurs within 3 to 5 weeks and recovery within 4 to 8 weeks.
215 Continuous maintenance therapy with 2 mg/day is instituted when the white blood cell count is
216 greater than 4,000 cells/mcL and the platelet count is greater than 100,000 cells/mcL. Dosage is
217 adjusted to between 1 and 3 mg/day depending upon the hematological response. It is desirable
218 to try to maintain a significant degree of bone marrow depression so as to keep the leukocyte
219 count in the range of 3,000 to 3,500 cells/mcL.

220 Hoogstraten et al have started treatment with 0.15 mg/kg/day for 7 days. This is followed by a
221 rest period of at least 14 days, but it may be as long as 5 to 6 weeks. Maintenance therapy is
222 started when the white blood cell and platelet counts are rising. The maintenance dose is
223 0.05 mg/kg/day or less and is adjusted according to the blood count.

224 Available evidence suggests that about one third to one half of the patients with multiple
225 myeloma show a favorable response to oral administration of the drug.

226 One study by Alexanian et al has shown that the use of ALKERAN in combination with
227 prednisone significantly improves the percentage of patients with multiple myeloma who achieve
228 palliation. One regimen has been to administer courses of ALKERAN at 0.25 mg/kg/day for
229 4 consecutive days (or, 0.20 mg/kg/day for 5 consecutive days) for a total dose of
230 1 mg/kg/course. These 4- to 5-day courses are then repeated every 4 to 6 weeks if the
231 granulocyte count and the platelet count have returned to normal levels.

232 It is to be emphasized that response may be very gradual over many months; it is important
233 that repeated courses or continuous therapy be given since improvement may continue slowly
234 over many months, and the maximum benefit may be missed if treatment is abandoned too soon.

235 In patients with moderate to severe renal impairment, currently available pharmacokinetic
236 data do not justify an absolute recommendation on dosage reduction to those patients, but it may
237 be prudent to use a reduced dose initially.

238 **Epithelial Ovarian Cancer:** One commonly employed regimen for the treatment of ovarian
239 carcinoma has been to administer ALKERAN at a dose of 0.2 mg/kg daily for 5 days as a single
240 course. Courses are repeated every 4 to 5 weeks depending upon hematologic tolerance.

241 **Administration Precautions:** Procedures for proper handling and disposal of anticancer
242 drugs should be considered. Several guidelines on this subject have been published.¹⁻⁸

243 There is no general agreement that all of the procedures recommended in the guidelines are
244 necessary or appropriate.

245

246 **HOW SUPPLIED**

247 ALKERAN is supplied as white, film-coated, round, biconvex tablets containing 2 mg
248 melphalan in amber glass bottles with child-resistant closures. One side is engraved with “GX
249 EH3” and the other side is engraved with an “A.”

250 Bottle of 50 (NDC 0173-0045-35).

251 **Store in a refrigerator, 2° to 8°C (36° to 46°F). Protect from light.**

252

253 **REFERENCES**

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