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PRESCRIBING INFORMATION

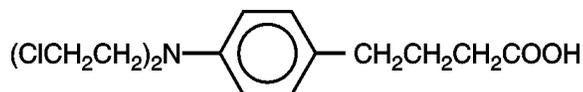
LEUKERAN[®]
(chlorambucil)
Tablets

WARNING

LEUKERAN (chlorambucil) can severely suppress bone marrow function. Chlorambucil is a carcinogen in humans. Chlorambucil is probably mutagenic and teratogenic in humans. Chlorambucil produces human infertility (see WARNINGS and PRECAUTIONS).

DESCRIPTION

LEUKERAN (chlorambucil) was first synthesized by Everett et al. It is a bifunctional alkylating agent of the nitrogen mustard type that has been found active against selected human neoplastic diseases. Chlorambucil is known chemically as 4-[bis(2-chlorethyl)amino]benzenebutanoic acid and has the following structural formula:



Chlorambucil hydrolyzes in water and has a pKa of 5.8.

LEUKERAN (chlorambucil) is available in tablet form for oral administration. Each film-coated tablet contains 2 mg chlorambucil and the inactive ingredients colloidal silicon dioxide, hypromellose, lactose (anhydrous), macrogol/PEG 400, microcrystalline cellulose, red iron oxide, stearic acid, titanium dioxide, and yellow iron oxide.

CLINICAL PHARMACOLOGY

Chlorambucil is rapidly and completely absorbed from the gastrointestinal tract. After single oral doses of 0.6 to 1.2 mg/kg, peak plasma chlorambucil levels (C_{max}) are reached within 1 hour and the terminal elimination half-life ($t_{1/2}$) of the parent drug is estimated at 1.5 hours.

Chlorambucil undergoes rapid metabolism to phenylacetic acid mustard, the major metabolite, and the combined chlorambucil and phenylacetic acid mustard urinary excretion is extremely low — less than 1% in 24 hours. In a study of 12 patients given single oral doses of 0.2 mg/kg of LEUKERAN, the mean dose (12 mg) adjusted (\pm SD) plasma chlorambucil C_{max} was 492 ± 160 ng/mL, the AUC was 883 ± 329 ng•h/mL, $t_{1/2}$ was 1.3 ± 0.5 hours, and the t_{max} was 0.83 ± 0.53 hours. For the major metabolite, phenylacetic acid mustard, the mean dose (12 mg) adjusted (\pm SD) plasma C_{max} was 306 ± 73 ng/mL, the AUC was 1204 ± 285 ng•h/mL, the $t_{1/2}$ was 1.8 ± 0.4 hours, and the t_{max} was 1.9 ± 0.7 hours.

Chlorambucil and its metabolites are extensively bound to plasma and tissue proteins. In vitro, chlorambucil is 99% bound to plasma proteins, specifically albumin. Cerebrospinal fluid levels

37 of chlorambucil have not been determined. Evidence of human teratogenicity suggests that the
38 drug crosses the placenta.

39 Chlorambucil is extensively metabolized in the liver primarily to phenylacetic acid mustard,
40 which has antineoplastic activity. Chlorambucil and its major metabolite spontaneously degrade
41 in vivo forming monohydroxy and dihydroxy derivatives. After a single dose of radiolabeled
42 chlorambucil (¹⁴C), approximately 15% to 60% of the radioactivity appears in the urine after
43 24 hours. Again, less than 1% of the urinary radioactivity is in the form of chlorambucil or
44 phenylacetic acid mustard. In summary, the pharmacokinetic data suggest that oral chlorambucil
45 undergoes rapid gastrointestinal absorption and plasma clearance and that it is almost completely
46 metabolized, having extremely low urinary excretion.

47 **INDICATIONS AND USAGE**

48 LEUKERAN (chlorambucil) is indicated in the treatment of chronic lymphatic (lymphocytic)
49 leukemia, malignant lymphomas including lymphosarcoma, giant follicular lymphoma, and
50 Hodgkin's disease. It is not curative in any of these disorders but may produce clinically useful
51 palliation.

52 **CONTRAINDICATIONS**

53 Chlorambucil should not be used in patients whose disease has demonstrated a prior resistance
54 to the agent. Patients who have demonstrated hypersensitivity to chlorambucil should not be
55 given the drug. There may be cross-hypersensitivity (skin rash) between chlorambucil and other
56 alkylating agents.

57 **WARNINGS**

58 Because of its carcinogenic properties, chlorambucil should not be given to patients with
59 conditions other than chronic lymphatic leukemia or malignant lymphomas. Convulsions,
60 infertility, leukemia, and secondary malignancies have been observed when chlorambucil was
61 employed in the therapy of malignant and non-malignant diseases.

62 There are many reports of acute leukemia arising in patients with both malignant and
63 non-malignant diseases following chlorambucil treatment. In many instances, these patients also
64 received other chemotherapeutic agents or some form of radiation therapy. The quantitation of
65 the risk of chlorambucil-induction of leukemia or carcinoma in humans is not possible.
66 Evaluation of published reports of leukemia developing in patients who have received
67 chlorambucil (and other alkylating agents) suggests that the risk of leukemogenesis increases
68 with both chronicity of treatment and large cumulative doses. However, it has proved impossible
69 to define a cumulative dose below which there is no risk of the induction of secondary
70 malignancy. The potential benefits from chlorambucil therapy must be weighed on an individual
71 basis against the possible risk of the induction of a secondary malignancy.

72 Chlorambucil has been shown to cause chromatid or chromosome damage in humans. Both
73 reversible and permanent sterility have been observed in both sexes receiving chlorambucil.

74 A high incidence of sterility has been documented when chlorambucil is administered to
75 prepubertal and pubertal males. Prolonged or permanent azoospermia has also been observed in
76 adult males. While most reports of gonadal dysfunction secondary to chlorambucil have related
77 to males, the induction of amenorrhea in females with alkylating agents is well documented and
78 chlorambucil is capable of producing amenorrhea. Autopsy studies of the ovaries from women
79 with malignant lymphoma treated with combination chemotherapy including chlorambucil have
80 shown varying degrees of fibrosis, vasculitis, and depletion of primordial follicles.

81 Rare instances of skin rash progressing to erythema multiforme, toxic epidermal necrolysis, or
82 Stevens-Johnson syndrome have been reported. Chlorambucil should be discontinued promptly
83 in patients who develop skin reactions.

84 **Pregnancy:** Pregnancy Category D. Chlorambucil can cause fetal harm when administered to a
85 pregnant woman. Unilateral renal agenesis has been observed in 2 offspring whose mothers
86 received chlorambucil during the first trimester. Urogenital malformations, including absence of
87 a kidney, were found in fetuses of rats given chlorambucil. There are no adequate and
88 well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient
89 becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to
90 the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

91 **PRECAUTIONS**

92 **General:** Many patients develop a slowly progressive lymphopenia during treatment. The
93 lymphocyte count usually rapidly returns to normal levels upon completion of drug therapy.
94 Most patients have some neutropenia after the third week of treatment and this may continue for
95 up to 10 days after the last dose. Subsequently, the neutrophil count usually rapidly returns to
96 normal. Severe neutropenia appears to be related to dosage and usually occurs only in patients
97 who have received a total dosage of 6.5 mg/kg or more in one course of therapy with continuous
98 dosing. About one quarter of all patients receiving the continuous-dose schedule, and one third of
99 those receiving this dosage in 8 weeks or less may be expected to develop severe neutropenia.

100 While it is not necessary to discontinue chlorambucil at the first evidence of a fall in
101 neutrophil count, it must be remembered that the fall may continue for 10 days after the last
102 dose, and that as the total dose approaches 6.5 mg/kg, there is a risk of causing irreversible bone
103 marrow damage. The dose of chlorambucil should be decreased if leukocyte or platelet counts
104 fall below normal values and should be discontinued for more severe depression.

105 Chlorambucil should **not** be given at full dosages before 4 weeks after a full course of
106 radiation therapy or chemotherapy because of the vulnerability of the bone marrow to damage
107 under these conditions. If the pretherapy leukocyte or platelet counts are depressed from bone
108 marrow disease process prior to institution of therapy, the treatment should be instituted at a
109 reduced dosage.

110 Persistently low neutrophil and platelet counts or peripheral lymphocytosis suggest bone
111 marrow infiltration. If confirmed by bone marrow examination, the daily dosage of chlorambucil
112 should not exceed 0.1 mg/kg. Chlorambucil appears to be relatively free from gastrointestinal

113 side effects or other evidence of toxicity apart from the bone marrow depressant action. In
114 humans, single oral doses of 20 mg or more may produce nausea and vomiting.

115 Children with nephrotic syndrome and patients receiving high pulse doses of chlorambucil
116 may have an increased risk of seizures. As with any potentially epileptogenic drug, caution
117 should be exercised when administering chlorambucil to patients with a history of seizure
118 disorder or head trauma, or who are receiving other potentially epileptogenic drugs.

119 Administration of live vaccines to immunocompromised patients should be avoided.

120 **Information for Patients:** Patients should be informed that the major toxicities of
121 chlorambucil are related to hypersensitivity, drug fever, myelosuppression, hepatotoxicity,
122 infertility, seizures, gastrointestinal toxicity, and secondary malignancies. Patients should never
123 be allowed to take the drug without medical supervision and should consult their physician if
124 they experience skin rash, bleeding, fever, jaundice, persistent cough, seizures, nausea, vomiting,
125 amenorrhea, or unusual lumps/masses. Women of childbearing potential should be advised to
126 avoid becoming pregnant.

127 **Laboratory Tests:** Patients must be followed carefully to avoid life-endangering damage to
128 the bone marrow during treatment. Weekly examination of the blood should be made to
129 determine hemoglobin levels, total and differential leukocyte counts, and quantitative platelet
130 counts. Also, during the first 3 to 6 weeks of therapy, it is recommended that white blood cell
131 counts be made 3 or 4 days after each of the weekly complete blood counts. Galton et al have
132 suggested that in following patients it is helpful to plot the blood counts on a chart at the same
133 time that body weight, temperature, spleen size, etc., are recorded. It is considered dangerous to
134 allow a patient to go more than 2 weeks without hematological and clinical examination during
135 treatment.

136 **Drug Interactions:** There are no known drug/drug interactions with chlorambucil.

137 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** See WARNINGS section for
138 information on carcinogenesis, mutagenesis, and impairment of fertility.

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

140 **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many
141 drugs are excreted in human milk and because of the potential for serious adverse reactions in
142 nursing infants from chlorambucil, a decision should be made whether to discontinue nursing or
143 to discontinue the drug, taking into account the importance of the drug to the mother.

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

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

151 **ADVERSE REACTIONS**

152 **Hematologic:** The most common side effect is bone marrow suppression, anemia, leukopenia,
153 neutropenia, thrombocytopenia, or pancytopenia. Although bone marrow suppression frequently
154 occurs, it is usually reversible if the chlorambucil is withdrawn early enough. However,
155 irreversible bone marrow failure has been reported.

156 **Gastrointestinal:** Gastrointestinal disturbances such as nausea and vomiting, diarrhea, and oral
157 ulceration occur infrequently.

158 **CNS:** Tremors, muscular twitching, myoclonia, confusion, agitation, ataxia, flaccid paresis, and
159 hallucinations have been reported as rare adverse experiences to chlorambucil which resolve
160 upon discontinuation of drug. Rare, focal and/or generalized seizures have been reported to occur
161 in both children and adults at both therapeutic daily doses and pulse-dosing regimens, and in
162 acute overdose (see PRECAUTIONS: General).

163 **Dermatologic:** Allergic reactions such as urticaria and angioneurotic edema have been
164 reported following initial or subsequent dosing. Skin hypersensitivity (including rare reports of
165 skin rash progressing to erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson
166 syndrome) has been reported (see WARNINGS).

167 **Miscellaneous:** Other reported adverse reactions include: pulmonary fibrosis, hepatotoxicity
168 and jaundice, drug fever, peripheral neuropathy, interstitial pneumonia, sterile cystitis, infertility,
169 leukemia, and secondary malignancies (see WARNINGS).

170 **OVERDOSAGE**

171 Reversible pancytopenia was the main finding of inadvertent overdoses of chlorambucil.
172 Neurological toxicity ranging from agitated behavior and ataxia to multiple grand mal seizures
173 has also occurred. As there is no known antidote, the blood picture should be closely monitored
174 and general supportive measures should be instituted, together with appropriate blood
175 transfusions, if necessary. Chlorambucil is not dialyzable.

176 Oral LD₅₀ single doses in mice are 123 mg/kg. In rats, a single intraperitoneal dose of
177 12.5 mg/kg of chlorambucil produces typical nitrogen-mustard effects; these include atrophy of
178 the intestinal mucous membrane and lymphoid tissues, severe lymphopenia becoming maximal
179 in 4 days, anemia, and thrombocytopenia. After this dose, the animals begin to recover within
180 3 days and appear normal in about a week, although the bone marrow may not become
181 completely normal for about 3 weeks. An intraperitoneal dose of 18.5 mg/kg kills about 50% of
182 the rats with development of convulsions. As much as 50 mg/kg has been given orally to rats as a
183 single dose, with recovery. Such a dose causes bradycardia, excessive salivation, hematuria,
184 convulsions, and respiratory dysfunction.

185 **DOSAGE AND ADMINISTRATION**

186 The usual oral dosage is 0.1 to 0.2 mg/kg body weight daily for 3 to 6 weeks as required. This
187 usually amounts to 4 to 10 mg per day for the average patient. The entire daily dose may be
188 given at one time. These dosages are for initiation of therapy or for short courses of treatment.
189 The dosage must be carefully adjusted according to the response of the patient and must be

190 reduced as soon as there is an abrupt fall in the white blood cell count. Patients with Hodgkin's
191 disease usually require 0.2 mg/kg daily, whereas patients with other lymphomas or chronic
192 lymphocytic leukemia usually require only 0.1 mg/kg daily. When lymphocytic infiltration of the
193 bone marrow is present, or when the bone marrow is hypoplastic, the daily dose should not
194 exceed 0.1 mg/kg (about 6 mg for the average patient).

195 Alternate schedules for the treatment of chronic lymphocytic leukemia employing
196 intermittent, biweekly, or once-monthly pulse doses of chlorambucil have been reported.
197 Intermittent schedules of chlorambucil begin with an initial single dose of 0.4 mg/kg. Doses are
198 generally increased by 0.1 mg/kg until control of lymphocytosis or toxicity is observed.
199 Subsequent doses are modified to produce mild hematologic toxicity. It is felt that the response
200 rate of chronic lymphocytic leukemia to the biweekly or once-monthly schedule of chlorambucil
201 administration is similar or better to that previously reported with daily administration and that
202 hematologic toxicity was less than or equal to that encountered in studies using daily
203 chlorambucil.

204 Radiation and cytotoxic drugs render the bone marrow more vulnerable to damage, and
205 chlorambucil should be used with particular caution within 4 weeks of a full course of radiation
206 therapy or chemotherapy. However, small doses of palliative radiation over isolated foci remote
207 from the bone marrow will not usually depress the neutrophil and platelet count. In these cases
208 chlorambucil may be given in the customary dosage.

209 It is presently felt that short courses of treatment are safer than continuous maintenance
210 therapy, although both methods have been effective. It must be recognized that continuous
211 therapy may give the appearance of "maintenance" in patients who are actually in remission and
212 have no immediate need for further drug. If maintenance dosage is used, it should not exceed
213 0.1 mg/kg daily and may well be as low as 0.03 mg/kg daily. A typical maintenance dose is 2 mg
214 to 4 mg daily, or less, depending on the status of the blood counts. It may, therefore, be desirable
215 to withdraw the drug after maximal control has been achieved, since intermittent therapy
216 reinstated at time of relapse may be as effective as continuous treatment.

217

218 Procedures for proper handling and disposal of anticancer drugs should be used. Several
219 guidelines on this subject have been published.¹⁻⁸

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

222 **HOW SUPPLIED**

223 Leukeran is supplied as brown, film-coated, round, biconvex tablets containing 2 mg
224 chlorambucil in amber glass bottles with child-resistant closures. One side is engraved with "GX
225 EG3" and the other side is engraved with an "L."

226 Bottle of 50 (NDC 0173-0635-35).

227 **Store in a refrigerator, 2° to 8°C (36° to 46°F).**

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