

1 **PRESCRIBING INFORMATION**

2 **MYLERAN[®]**

3 **(busulfan)**

4 **2-mg Scored Tablets**

5
6 **WARNING**

7 *MYLERAN is a potent drug. It should not be used unless a diagnosis of chronic myelogenous*
8 *leukemia has been adequately established and the responsible physician is knowledgeable in*
9 *assessing response to chemotherapy.*

10 *MYLERAN can induce severe bone marrow hypoplasia. Reduce or discontinue the dosage*
11 *immediately at the first sign of any unusual depression of bone marrow function as reflected by an*
12 *abnormal decrease in any of the formed elements of the blood. A bone marrow examination should*
13 *be performed if the bone marrow status is uncertain.*

14 *SEE WARNINGS FOR INFORMATION REGARDING BUSULFAN-INDUCED*
15 *LEUKEMOGENESIS IN HUMANS.*

16
17 **DESCRIPTION**

18 MYLERAN (busulfan) is a bifunctional alkylating agent. Busulfan is known chemically as 1,4-
19 butanediol dimethanesulfonate and has the following structural formula:



23 Busulfan is *not* a structural analog of the nitrogen mustards. MYLERAN is available in tablet
24 form for oral administration. Each scored tablet contains 2 mg busulfan and the inactive ingredients
25 magnesium stearate and sodium chloride.

26 The activity of busulfan in chronic myelogenous leukemia was first reported by D.A.G. Galton in
27 1953.

28
29 **CLINICAL PHARMACOLOGY**

30 **Studies with ³⁵S-busulfan:** Following the intravenous administration of a single therapeutic
31 dose of ³⁵S-busulfan, there was rapid disappearance of radioactivity from the blood; 90% to 95% of
32 the ³⁵S-label disappeared within 3 to 5 minutes after injection. Thereafter, a constant, low level of
33 radioactivity (1% to 3% of the injected dose) was maintained during the subsequent 48-hour period
34 of observation. Following the oral administration of ³⁵S-busulfan, there was a lag period of ½ to
35 2 hours prior to the detection of radioactivity in the blood. However, at 4 hours the (low) level of
36 circulating radioactivity was comparable to that obtained following intravenous administration.

37 After either oral or intravenous administration of ³⁵S-busulfan to humans, 45% to 60% of the
38 radioactivity was recovered in the urine in the 48 hours after administration; the majority of the
39 total urinary excretion occurred in the first 24 hours. In humans, over 95% of the urinary sulfur-35
40 occurs as ³⁵S-methanesulfonic acid.

41 The fact that urinary recovery of sulfur-35 was equivalent, irrespective of whether the drug was
42 given intravenously or orally, suggests virtually complete absorption by the oral route.

43 **Studies with ¹⁴C-busulfan:** Oral and intravenous administration of 1,4-¹⁴C-busulfan showed the
44 same rapid initial disappearance of plasma radioactivity with a subsequent low-level plateau as
45 observed following the administration of ³⁵S-labeled drug. Cumulative radioactivity in the urine
46 after 48 hours was 25% to 30% of the administered dose (contrasting with 45% to 60% for
47 ³⁵S-busulfan) and suggests a slower excretion of the alkylating portion of the molecule and its
48 metabolites than for the sulfonoxymethyl moieties. Regardless of the route of administration,
49 1,4-¹⁴C-busulfan yielded a complex mixture of at least 12 radiolabeled metabolites in urine; the
50 main metabolite being 3-hydroxytetrahydrothiophene-1,1-dioxide.

51 **Studies with ³H-busulfan:** Human pharmacokinetic studies have been conducted employing
52 busulfan labeled with tritium on the tetramethylene chain. These experiments confirmed a rapid
53 initial clearance of the radioactivity from plasma, irrespective of whether the drug was given orally
54 or intravenously, and showed a gradual accumulation of radioactivity in the plasma after repeated
55 doses. Urinary excretion of less than 50% of the total dose given suggested a slow elimination of
56 the metabolic products from the body.

57 **Pharmacokinetics in Hemodialysis Patients:** The impact of hemodialysis on the clearance of
58 busulfan was determined in a patient with chronic renal failure undergoing autologous stem cell
59 transplantation. The apparent oral clearance of busulfan during a 4-hour hemodialysis session was
60 increased by 65%, but the 24-hour oral clearance of busulfan was increased by only 11%.

61 The incidence of veno-occlusive disease was higher (33.3% versus 3.0%) in patients with
62 busulfan $AUC_{0-6hr} > 1,500 \mu M \cdot min$ ($C_{ss} > 900 \text{ mcg/L}$) compared to patients with busulfan AUC_{0-6hr}
63 $< 1,500 \mu M \cdot min$ ($C_{ss} < 900 \text{ mcg/L}$) (see WARNINGS).

64 **Drug Interactions:** Itraconazole reduced busulfan clearance by up to 25% in patients receiving
65 itraconazole compared to patients who did not receive itraconazole. Higher busulfan exposure due
66 to concomitant itraconazole could lead to toxic plasma levels in some patients.. Fluconazole had no
67 effect on the clearance of busulfan. Patients treated with concomitant cyclophosphamide and
68 busulfan with phenytoin pretreatment have increased cyclophosphamide and busulfan clearance,
69 which may lead to decreased concentrations of both cyclophosphamide and busulfan. However,
70 busulfan clearance may be reduced in the presence of cyclophosphamide alone, presumably due to
71 competition for glutathione.

72 Diazepam had no effect on the clearance of busulfan.

73 No information is available regarding the penetration of busulfan into brain or cerebrospinal
74 fluid.

75 **Biochemical Pharmacology:** In aqueous media, busulfan undergoes a wide range of
76 nucleophilic substitution reactions. While this chemical reactivity is relatively non-specific,
77 alkylation of the DNA is felt to be an important biological mechanism for its cytotoxic effect.
78 Coliphage T7 exposed to busulfan was found to have the DNA crosslinked by intrastrand
79 crosslinkages, but no interstrand linkages were found.

80 The metabolic fate of busulfan has been studied in rats and humans using ^{14}C - and ^{35}S -labeled
81 materials. In humans, as in the rat, almost all of the radioactivity in ^{35}S -labeled busulfan is excreted
82 in the urine in the form of ^{35}S -methanesulfonic acid. No unchanged drug was found in human urine,
83 although a small amount has been reported in rat urine. Roberts and Warwick demonstrated that the
84 formation of methanesulfonic acid in vivo in the rat is not due to a simple hydrolysis of busulfan to
85 1,4-butanediol, since only about 4% of 2,3- ^{14}C -busulfan was excreted as carbon dioxide, whereas
86 2,3- ^{14}C -1,4-butanediol was converted almost exclusively to carbon dioxide. The predominant
87 reaction of busulfan in the rat is the alkylation of sulfhydryl groups (particularly cysteine and
88 cysteine-containing compounds) to produce a cyclic sulfonium compound which is the precursor of
89 the major urinary metabolite of the 4-carbon portion of the molecule,
90 3-hydroxytetrahydrothiophene-1,1-dioxide. This has been termed a “sulfur-stripping” action of
91 busulfan and it may modify the function of certain sulfur-containing amino acids, polypeptides, and

92 proteins; whether this action makes an important contribution to the cytotoxicity of busulfan is
93 unknown.

94 The biochemical basis for acquired resistance to busulfan is largely a matter of speculation.
95 Although altered transport of busulfan into the cell is one possibility, increased intracellular
96 inactivation of the drug before it reaches the DNA is also possible. Experiments with other
97 alkylating agents have shown that resistance to this class of compounds may reflect an acquired
98 ability of the resistant cell to repair alkylation damage more effectively.

99 **Clinical Studies:** Although not curative, busulfan reduces the total granulocyte mass, relieves
100 symptoms of the disease, and improves the clinical state of the patient. Approximately 90% of
101 adults with previously untreated chronic myelogenous leukemia will obtain hematologic remission
102 with regression or stabilization of organomegaly following the use of busulfan. It has been shown to
103 be superior to splenic irradiation with respect to survival times and maintenance of hemoglobin
104 levels, and to be equivalent to irradiation at controlling splenomegaly.

105 It is not clear whether busulfan unequivocally prolongs the survival of responding patients
106 beyond the 31 months experienced by an untreated group of historical controls. Median survival
107 figures of 31 to 42 months have been reported for several groups of patients treated with busulfan,
108 but concurrent control groups of comparable, untreated patients are not available. The median
109 survival figures reported from different studies will be influenced by the percentage of “poor risk”
110 patients initially entered into the particular study. Patients who are alive 2 years following the
111 diagnosis of chronic myelogenous leukemia, and who have been treated during that period with
112 busulfan, are estimated to have a mean annual mortality rate during the second to fifth year which is
113 approximately two thirds that of patients who received either no treatment, conventional x-ray or
114 ³²P-irradiation, or chemotherapy with minimally active drugs.

115 Busulfan is clearly less effective in patients with chronic myelogenous leukemia who lack the
116 Philadelphia (Ph¹) chromosome. Also, the so-called “juvenile” type of chronic myelogenous
117 leukemia, typically occurring in young children and associated with the absence of a Philadelphia
118 chromosome, responds poorly to busulfan. The drug is of no benefit in patients whose chronic
119 myelogenous leukemia has entered a “blastic” phase.

120 MYLERAN should not be used in patients whose chronic myelogenous leukemia has
121 demonstrated prior resistance to this drug.

122 MYLERAN is of no value in chronic lymphocytic leukemia, acute leukemia, or in the “blastic
123 crisis” of chronic myelogenous leukemia.

124

125 **INDICATIONS AND USAGE**

126 MYLERAN (busulfan) is indicated for the palliative treatment of chronic myelogenous
127 (myeloid, myelocytic, granulocytic) leukemia.

128

129 **CONTRAINDICATIONS**

130 MYLERAN is contraindicated in patients in whom a definitive diagnosis of chronic
131 myelogenous leukemia has not been firmly established.

132 MYLERAN is contraindicated in patients who have previously suffered a hypersensitivity
133 reaction to busulfan or any other component of the preparation.

134

135 **WARNINGS**

136 The most frequent, serious side effect of treatment with busulfan is the induction of bone marrow
137 failure (which may or may not be anatomically hypoplastic) resulting in severe pancytopenia. The
138 pancytopenia caused by busulfan may be more prolonged than that induced with other alkylating
139 agents. It is generally felt that the usual cause of busulfan-induced pancytopenia is the failure to
140 stop administration of the drug soon enough; individual idiosyncrasy to the drug does not seem to
141 be an important factor. *MYLERAN should be used with extreme caution and exceptional vigilance*
142 *in patients whose bone marrow reserve may have been compromised by prior irradiation or*
143 *chemotherapy, or whose marrow function is recovering from previous cytotoxic therapy.* Although
144 recovery from busulfan-induced pancytopenia may take from 1 month to 2 years, this complication
145 is potentially reversible, and the patient should be vigorously supported through any period of
146 severe pancytopenia.

147 A rare, important complication of busulfan therapy is the development of bronchopulmonary
148 dysplasia with pulmonary fibrosis. Symptoms have been reported to occur within 8 months to
149 10 years after initiation of therapy—the average duration of therapy being 4 years. The histologic
150 findings associated with “busulfan lung” mimic those seen following pulmonary irradiation.
151 Clinically, patients have reported the insidious onset of cough, dyspnea, and low-grade fever. In
152 some cases, however, onset of symptoms may be acute. Pulmonary function studies have revealed

153 diminished diffusion capacity and decreased pulmonary compliance. It is important to exclude more
154 common conditions (such as opportunistic infections or leukemic infiltration of the lungs) with
155 appropriate diagnostic techniques. If measures such as sputum cultures, virologic studies, and
156 exfoliative cytology fail to establish an etiology for the pulmonary infiltrates, lung biopsy may be
157 necessary to establish the diagnosis. Treatment of established busulfan-induced pulmonary fibrosis
158 is unsatisfactory; in most cases the patients have died within 6 months after the diagnosis was
159 established. There is no specific therapy for this complication. MYLERAN should be discontinued
160 if this lung toxicity develops. The administration of corticosteroids has been suggested, but the
161 results have not been impressive or uniformly successful.

162 Busulfan may cause cellular dysplasia in many organs in addition to the lung. Cytologic
163 abnormalities characterized by giant, hyperchromatic nuclei have been reported in lymph nodes,
164 pancreas, thyroid, adrenal glands, liver, and bone marrow. This cytologic dysplasia may be severe
165 enough to cause difficulty in interpretation of exfoliative cytologic examinations from the lung,
166 bladder, breast, and the uterine cervix.

167 In addition to the widespread epithelial dysplasia that has been observed during busulfan therapy,
168 chromosome aberrations have been reported in cells from patients receiving busulfan.

169 Busulfan is mutagenic in mice and, possibly, in humans.

170 Malignant tumors and acute leukemias have been reported in patients who have received
171 busulfan therapy, and this drug may be a human carcinogen. The World Health Organization has
172 concluded that there is a causal relationship between busulfan exposure and the development of
173 secondary malignancies. Four cases of acute leukemia occurred among 243 patients treated with
174 busulfan as adjuvant chemotherapy following surgical resection of bronchogenic carcinoma. All 4
175 cases were from a subgroup of 19 of these 243 patients who developed pancytopenia while taking
176 busulfan 5 to 8 years before leukemia became clinically apparent. These findings suggest that
177 busulfan is leukemogenic, although its mode of action is uncertain.

178 Ovarian suppression and amenorrhea with menopausal symptoms commonly occur during
179 busulfan therapy in premenopausal patients. Busulfan has been associated with ovarian failure
180 including failure to achieve puberty in females. Busulfan interferes with spermatogenesis in
181 experimental animals, and there have been clinical reports of sterility, azoospermia, and testicular
182 atrophy in male patients.

183 Hepatic veno-occlusive disease, which may be life threatening, has been reported in patients
184 receiving busulfan, usually in combination with cyclophosphamide or other chemotherapeutic
185 agents prior to bone marrow transplantation. Possible risk factors for the development of hepatic
186 veno-occlusive disease include: total busulfan dose exceeding 16 mg/kg based on ideal body
187 weight, and concurrent use of multiple alkylating agents (see CLINICAL PHARMACOLOGY and
188 Drug Interactions).

189 A clear cause-and-effect relationship with busulfan has not been demonstrated. Periodic
190 measurement of serum transaminases, alkaline phosphatase, and bilirubin is indicated for early
191 detection of hepatotoxicity. A reduced incidence of hepatic veno-occlusive disease and other
192 regimen-related toxicities have been observed in patients treated with high-dose MYLERAN and
193 cyclophosphamide when the first dose of cyclophosphamide has been delayed for >24 hours after
194 the last dose of busulfan (see CLINICAL PHARMACOLOGY and Drug Interactions).

195 Cardiac tamponade has been reported in a small number of patients with thalassemia (2% in one
196 series) who received busulfan and cyclophosphamide as the preparatory regimen for bone marrow
197 transplantation. In this series, the cardiac tamponade was often fatal. Abdominal pain and vomiting
198 preceded the tamponade in most patients.

199 **Pregnancy:** Pregnancy Category D. Busulfan may cause fetal harm when administered to a
200 pregnant woman. Although there have been a number of cases reported where apparently normal
201 children have been born after busulfan treatment during pregnancy, one case has been cited where a
202 malformed baby was delivered by a mother treated with busulfan. During the pregnancy that
203 resulted in the malformed infant, the mother received x-ray therapy early in the first trimester,
204 mercaptopurine until the third month, then busulfan until delivery. In pregnant rats, busulfan
205 produces sterility in both male and female offspring due to the absence of germinal cells in testes
206 and ovaries. Germinal cell aplasia or sterility in offspring of mothers receiving busulfan during
207 pregnancy has not been reported in humans. There are no adequate and well-controlled studies in
208 pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while
209 taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of
210 childbearing potential should be advised to avoid becoming pregnant.

211

212 **PRECAUTIONS**

213 **General:** The most consistent, dose-related toxicity is bone marrow suppression. This may be
214 manifest by anemia, leukopenia, thrombocytopenia, or any combination of these. It is imperative
215 that patients be instructed to report promptly the development of fever, sore throat, signs of local
216 infection, bleeding from any site, or symptoms suggestive of anemia. Any one of these findings
217 may indicate busulfan toxicity; however, they may also indicate transformation of the disease to an
218 acute “blastic” form. Since busulfan may have a delayed effect, it is important to withdraw the
219 medication temporarily at the first sign of an abnormally large or exceptionally rapid fall in any of
220 the formed elements of the blood. *Patients should never be allowed to take the drug without close*
221 *medical supervision.*

222 Seizures have been reported in patients receiving busulfan. As with any potentially epileptogenic
223 drug, caution should be exercised when administering busulfan to patients with a history of seizure
224 disorder, head trauma, or receiving other potentially epileptogenic drugs. Some investigators have
225 used prophylactic anticonvulsant therapy in this setting.

226 **Information for Patients:** Patients beginning therapy with busulfan should be informed of the
227 importance of having periodic blood counts and to immediately report any unusual fever or
228 bleeding. Aside from the major toxicity of myelosuppression, patients should be instructed to report
229 any difficulty in breathing, persistent cough, or congestion. They should be told that diffuse
230 pulmonary fibrosis is an infrequent, but serious and potentially life-threatening complication of
231 long-term busulfan therapy. Patients should be alerted to report any signs of abrupt weakness,
232 unusual fatigue, anorexia, weight loss, nausea and vomiting, and melanoderma that could be
233 associated with a syndrome resembling adrenal insufficiency. Patients should never be allowed to
234 take the drug without medical supervision and they should be informed that other encountered
235 toxicities to busulfan include infertility, amenorrhea, skin hyperpigmentation, drug hypersensitivity,
236 dryness of the mucous membranes, and rarely, cataract formation. Women of childbearing potential
237 should be advised to avoid becoming pregnant. The increased risk of a second malignancy should
238 be explained to the patient.

239 **Laboratory Tests:** It is recommended that evaluation of the hemoglobin or hematocrit, total
240 white blood cell count and differential count, and quantitative platelet count be obtained weekly
241 while the patient is on busulfan therapy. In cases where the cause of fluctuation in the formed
242 elements of the peripheral blood is obscure, bone marrow examination may be useful for evaluation
243 of marrow status. A decision to increase, decrease, continue, or discontinue a given dose of

244 busulfan must be based not only on the absolute hematologic values, but also on the rapidity with
245 which changes are occurring. The dosage of busulfan may need to be reduced if this agent is
246 combined with other drugs whose primary toxicity is myelosuppression. Occasional patients may be
247 unusually sensitive to busulfan administered at standard dosage and suffer neutropenia or
248 thrombocytopenia after a relatively short exposure to the drug. Busulfan should not be used where
249 facilities for complete blood counts, including quantitative platelet counts, are not available at
250 weekly (or more frequent) intervals.

251 **Drug Interactions:** Busulfan may cause additive myelosuppression when used with other
252 myelosuppressive drugs.

253 In one study, 12 of approximately 330 patients receiving continuous busulfan and thioguanine
254 therapy for treatment of chronic myelogenous leukemia were found to have portal hypertension and
255 esophageal varices associated with abnormal liver function tests. Subsequent liver biopsies were
256 performed in 4 of these patients, all of which showed evidence of nodular regenerative hyperplasia.
257 Duration of combination therapy prior to the appearance of esophageal varices ranged from 6 to
258 45 months. With the present analysis of the data, no cases of hepatotoxicity have appeared in the
259 busulfan-alone arm of the study. Long-term continuous therapy with thioguanine and busulfan
260 should be used with caution.

261 Busulfan-induced pulmonary toxicity may be additive to the effects produced by other cytotoxic
262 agents.

263 The concomitant systemic administration of itraconazole to patients receiving high-dose
264 MYLERAN may result in reduced busulfan clearance (see CLINICAL PHARMACOLOGY).
265 Patients should be monitored for signs of busulfan toxicity when itraconazole is used concomitantly
266 with MYLERAN.

267 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** See WARNINGS section. The
268 World Health Organization has concluded that there is a causal relationship between busulfan
269 exposure and the development of secondary malignancies.

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

271 **Nonteratogenic Effects:** There have been reports in the literature of small infants being born
272 after the mothers received busulfan during pregnancy, in particular, during the third trimester. One
273 case was reported where an infant had mild anemia and neutropenia at birth after busulfan was
274 administered to the mother from the eighth week of pregnancy to term.

275 **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because of the
276 potential for tumorigenicity shown for busulfan in animal and human studies, a decision should be
277 made whether to discontinue nursing or to discontinue the drug, taking into account the importance
278 of the drug to the mother.

279 **Pediatric Use:** See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION
280 sections.

281

282 **ADVERSE REACTIONS**

283 **Hematological Effects:** The most frequent, serious, toxic effect of busulfan is dose-related
284 myelosuppression resulting in leukopenia, thrombocytopenia, and anemia. Myelosuppression is
285 most frequently the result of a failure to discontinue dosage in the face of an undetected decrease in
286 leukocyte or platelet counts.

287 Aplastic anemia (sometimes irreversible) has been reported rarely, often following long-term
288 conventional doses and also high doses of MYLERAN.

289 **Pulmonary:** Interstitial pulmonary fibrosis has been reported rarely, but it is a clinically
290 significant adverse effect when observed and calls for immediate discontinuation of further
291 administration of the drug. The role of corticosteroids in arresting or reversing the fibrosis has been
292 reported to be beneficial in some cases and without effect in others.

293 **Cardiac:** Cardiac tamponade has been reported in a small number of patients with thalassemia who
294 received busulfan and cyclophosphamide as the preparatory regimen for bone marrow
295 transplantation (see WARNINGS).

296 One case of endocardial fibrosis has been reported in a 79-year-old woman who received a total
297 dose of 7,200 mg of busulfan over a period of 9 years for the management of chronic myelogenous
298 leukemia. At autopsy, she was found to have endocardial fibrosis of the left ventricle in addition to
299 interstitial pulmonary fibrosis.

300 **Ocular:** Busulfan is capable of inducing cataracts in rats and there have been several reports
301 indicating that this is a rare complication in humans.

302 **Dermatologic:** Hyperpigmentation is the most common adverse skin reaction and occurs in 5% to
303 10% of patients, particularly those with a dark complexion.

304 **Metabolic:** In a few cases, a clinical syndrome closely resembling adrenal insufficiency and
305 characterized by weakness, severe fatigue, anorexia, weight loss, nausea and vomiting, and

306 melanoderma has developed after prolonged busulfan therapy. The symptoms have sometimes been
307 reversible when busulfan was withdrawn. Adrenal responsiveness to exogenously administered
308 ACTH has usually been normal. However, pituitary function testing with metyrapone revealed a
309 blunted urinary 17-hydroxycorticosteroid excretion in 2 patients. Following the discontinuation of
310 busulfan (which was associated with clinical improvement), rechallenge with metyrapone revealed
311 normal pituitary-adrenal function.

312 Hyperuricemia and/or hyperuricosuria are not uncommon in patients with chronic myelogenous
313 leukemia. Additional rapid destruction of granulocytes may accompany the initiation of
314 chemotherapy and increase the urate pool. Adverse effects can be minimized by increased
315 hydration, urine alkalinization, and the prophylactic administration of a xanthine oxidase inhibitor
316 such as allopurinol.

317 **Hepatic Effects:** Esophageal varices have been reported in patients receiving continuous busulfan
318 and thioguanine therapy for treatment of chronic myelogenous leukemia (see PRECAUTIONS:
319 Drug Interactions). Hepatic veno-occlusive disease has been observed in patients receiving busulfan
320 (see WARNINGS).

321 **Miscellaneous:** Other reported adverse reactions include: urticaria, erythema multiforme,
322 erythema nodosum, alopecia, porphyria cutanea tarda, excessive dryness and fragility of the skin
323 with anhidrosis, dryness of the oral mucous membranes and cheilosis, gynecomastia, cholestatic
324 jaundice, and myasthenia gravis. Most of these are single case reports, and in many, a clear
325 cause-and-effect relationship with busulfan has not been demonstrated.

326 Seizures (see PRECAUTIONS: General) have been observed in patients receiving higher than
327 recommended doses of busulfan.

328 **Observed During Clinical Practice:** The following events have been identified during post-
329 approval use of busulfan. Because they are reported voluntarily from a population of unknown size,
330 estimates of frequency cannot be made. These events have been chosen for inclusion due to a
331 combination of their seriousness, frequency of reporting, or potential causal connection to busulfan.

332 **Blood and Lymphatic:** Aplastic anemia.

333 **Eye:** Cataracts, corneal thinning, lens changes.

334 **Hepatobiliary Tract and Pancreas:** Centrilobular sinusoidal fibrosis, hepatic veno-occlusive
335 disease, hepatocellular atrophy, hepatocellular necrosis, hyperbilirubinemia (see WARNINGS).

336 **Non-site Specific:** Infection, mucositis, sepsis.

337 **Respiratory:** Pneumonia.

338 **Skin:** Rash. An increased local cutaneous reaction has been observed in patients receiving
339 radiotherapy soon after busulfan.

340

341 **OVERDOSAGE**

342 There is no known antidote to busulfan. The principal toxic effects are bone marrow depression
343 and pancytopenia. The hematologic status should be closely monitored and vigorous supportive
344 measures instituted if necessary. Induction of vomiting or gastric lavage followed by administration
345 of charcoal would be indicated if ingestion were recent. Dialysis may be considered in the
346 management of overdose as there is 1 report of successful dialysis of busulfan (see
347 CLINICALPHARMACOLOGY).

348 Gastrointestinal toxicity with mucositis, nausea, vomiting, and diarrhea has been observed when
349 MYLERAN was used in association with bone marrow transplantation.

350 Oral LD₅₀ single doses in mice are 120 mg/kg. Two distinct types of toxic response are seen at
351 median lethal doses given intraperitoneally. Within a matter of hours there are signs of stimulation
352 of the central nervous system with convulsions and death on the first day. Mice are more sensitive
353 to this effect than are rats. With doses at the LD₅₀ there is also delayed death due to damage to the
354 bone marrow. At 3 times the LD₅₀, atrophy of the mucosa of the large intestine is found after a
355 week, whereas that of the small intestine is little affected. After doses in the order of 10 times those
356 used therapeutically were added to the diet of rats, irreversible cataracts were produced after several
357 weeks. Small doses had no such effect.

358

359 **DOSAGE AND ADMINISTRATION**

360 Busulfan is administered orally. The usual adult dose range for *remission induction* is 4 to 8 mg,
361 total dose, daily. Dosing on a weight basis is the same for both pediatric patients and adults,
362 approximately 60 mcg/kg of body weight or 1.8 mg/m² of body surface, daily. Since the rate of fall
363 of the leukocyte count is dose related, daily doses exceeding 4 mg per day should be reserved for
364 patients with the most compelling symptoms; the greater the total daily dose, the greater is the
365 possibility of inducing bone marrow aplasia.

366 A decrease in the leukocyte count is not usually seen during the first 10 to 15 days of treatment;
367 the leukocyte count may actually increase during this period and it should not be interpreted as

368 resistance to the drug, nor should the dose be increased. Since the leukocyte count may continue to
369 fall for more than 1 month after discontinuing the drug, it is important that busulfan be discontinued
370 *prior* to the total leukocyte count falling into the normal range. When the total leukocyte count has
371 declined to approximately 15,000/mcL, the drug should be withheld.

372 With a constant dose of busulfan, the total leukocyte count declines exponentially; a weekly plot
373 of the leukocyte count on semi-logarithmic graph paper aids in predicting the time when therapy
374 should be discontinued. With the recommended dose of busulfan, a normal leukocyte count is
375 usually achieved in 12 to 20 weeks.

376 During remission, the patient is examined at monthly intervals and treatment resumed with the
377 induction dosage when the total leukocyte count reaches approximately 50,000/mcL. When
378 remission is shorter than 3 months, maintenance therapy of 1 to 3 mg daily may be advisable in
379 order to keep the hematological status under control and prevent rapid relapse.

380 Procedures for proper handling and disposal of anticancer drugs should be considered. Several
381 guidelines on this subject have been published.¹⁻⁸

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

384

385 **HOW SUPPLIED**

386 White, scored tablets containing 2 mg busulfan, imprinted with “MYLERAN” and “K2A” on
387 each tablet; bottle of 25 (NDC 0173-0713-25).

388 **Store at 15° to 25°C (59° to 77°F) in a dry place.**

389

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