

1 **PRESCRIBING INFORMATION**

2 **MYLERAN[®]**

3 **(busulfan)**

4 **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 form
24 for oral administration. Each film-coated tablet contains 2 mg busulfan and the inactive ingredients
25 hypromellose, lactose (anhydrous), magnesium stearate, pregelatinized starch, triacetin, and titanium
26 dioxide.

27 The activity of busulfan in chronic myelogenous leukemia was first reported by D.A.G. Galton in
28 1953.

29
30 **CLINICAL PHARMACOLOGY**

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31 Busulfan is a small, highly lipophilic molecule that easily crosses the blood brain barrier.
32 Following absorption, 32% and 47% of busulfan are bound to plasma proteins and red blood cells,
33 respectively.

34 Busulfan absorption from the gastrointestinal tract is essentially complete. This has been
35 demonstrated in radioactive studies after both intravenous and oral administration of ³⁵S-busulfan,
36 ¹⁴C-busulfan, and ³H-busulfan. Following intravenous administration of a single therapeutic dose of
37 ³⁵S-busulfan, there was rapid disappearance of radioactivity from the blood and 90% to 95% of the
38 ³⁵S-label disappeared within 3 to 5 minutes after injection. After either oral or intravenous
39 administration of ³⁵S-busulfan, 45% to 60% of the radioactivity was recovered in the urine in the
40 48 hours after administration; the majority of the total urinary excretion occurring in the first 24 hours.
41 Over 95% of the urinary ³⁵S-label occurs as ³⁵S-methanesulfonic acid. Oral and intravenous
42 administration of 1,4-¹⁴C-busulfan showed the same rapid initial disappearance of plasma
43 radioactivity as observed following the administration of ³⁵S-labeled drug. Cumulative radioactivity
44 in the urine after 48 hours was 25% to 30% of the administered dose (contrasting with 45% to 60%
45 for ³⁵S-busulfan), and suggests a slower excretion of the alkylating portion of the molecule and its
46 metabolites than for the sulfonoxymethyl moieties. Regardless of the route of administration,
47 1,4-¹⁴C-busulfan yielded a complex mixture of at least 12 radiolabeled metabolites in urine; the main
48 metabolite being 3-hydroxytetrahydrothiophene-1,1-dioxide. Pharmacokinetic studies employing ³H-
49 busulfan labeled on the tetramethylene chain confirmed a rapid initial clearance of the radioactivity
50 from plasma, irrespective of whether the drug was given orally or intravenously.

51 A study compared a 2-mg single IV bolus injection to a single oral dose of a 2-mg tablet of
52 nonradioactive busulfan in 8 adult patients 13 to 60 years of age. The study demonstrated that the
53 mean ? SD absolute bioavailability was 80% ? 20% in adults. However, the absolute bioavailability
54 for 8 children 1.5 to 6 years of age was 68% ? 31%.

55 In another study of 2, 4, and 6 mg of busulfan, given as a single oral dose on consecutive days
56 (starting with the lowest dose) in 5 adult patients, the mean dose-normalized (to 2 mg dose) area
57 under the plasma concentration-time curve (AUC) was about 130 ng?hr/mL, while the mean intra- and
58 inter-patient variability was about 16% and 21%, respectively. Busulfan was eliminated with a
59 plasma terminal elimination half-life ($t_{1/2}$) of about 2.6 hours, and demonstrated linear kinetics within
60 the range of 2 to 6 mg for both the maximum plasma concentration (C_{max}) and AUC. The mean C_{max} for
61 the 2-, 4-, and 6-mg doses (after dose normalization to 2 mg) was about 30 ng/mL. A recent study of 4

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62 to 8 mg as single oral doses in 12 patients showed that the mean \pm SD C_{\max} (after dose normalization
63 to 4 mg) was 68.2 \pm 24.4 ng/mL, occurring at about 0.9 hours and the mean \pm SD AUC (after dose
64 normalization to 4 mg) was 269 \pm 62 ng \cdot hr/mL. These results are consistent with previous results. In
65 addition, the mean \pm SD elimination half-life was 2.69 \pm 0.49 hours.

66 The elimination of busulfan appears to be independent of renal function. This probably reflects the
67 extensive metabolism of the drug in the liver, since less than 2% of the administered dose is excreted
68 in the urine unchanged within 24 hours. The drug is metabolized by enzymatic activity to at least
69 12 metabolites, among which tetrahydrothiophene, tetrahydrothiophene 12-oxide, sulfolane, and
70 3-hydroxysulfolane were identified. These metabolites do not have cytotoxic activity.

71 There is no experience with the use of dialysis in an attempt to modify the clinical toxicity of
72 busulfan. One technical difficulty would derive from the extremely poor water solubility of busulfan.
73 Additionally, all studies of the metabolism of busulfan employing radiolabeled materials indicate
74 rapid chemical reactivity of the parent compound with prolonged retention of some of the metabolites
75 (particularly the metabolites arising from the “alkylating” portion of the molecule). The effectiveness
76 of dialysis at removing significant quantities of unreacted drug would be expected to be minimal in
77 such a situation.

78 Currently, there are no available data on the effect of food on busulfan bioavailability.

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

84 The metabolic fate of busulfan has been studied in rats and humans using ¹⁴C- and ³⁵S-labeled
85 materials. In humans, as in the rat, almost all of the radioactivity in ³⁵S-labeled busulfan is excreted in
86 the urine in the form of ³⁵S-methanesulfonic acid. Roberts and Warwick demonstrated that the
87 formation of methanesulfonic acid in vivo in the rat is not due to a simple hydrolysis of busulfan to
88 1,4-butanediol, since only about 4% of 2,3-¹⁴C-busulfan was excreted as carbon dioxide, whereas
89 2,3-¹⁴C-1,4-butanediol was converted almost exclusively to carbon dioxide. The predominant
90 reaction of busulfan in the rat is the alkylation of sulfhydryl groups (particularly cysteine and
91 cysteine-containing compounds) to produce a cyclic sulfonium compound which is the precursor of

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92 the major urinary metabolite of the 4-carbon portion of the molecule, 3-hydroxytetrahydrothiophene-
93 1,1-dioxide. This has been termed a “sulfur-stripping” action of busulfan and it may modify the
94 function of certain sulfur-containing amino acids, polypeptides, and proteins; whether this action
95 makes an important contribution to the cytotoxicity of busulfan is unknown.

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

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

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

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

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

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

126

127 **INDICATIONS AND USAGE**

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

130

131 **CONTRAINDICATIONS**

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

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

136

137 **WARNINGS**

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

149 A rare, important complication of busulfan therapy is the development of bronchopulmonary
150 dysplasia with pulmonary fibrosis. Symptoms have been reported to occur within 8 months to
151 10 years after initiation of therapy—the average duration of therapy being 4 years. The histologic

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152 findings associated with “busulfan lung” mimic those seen following pulmonary irradiation.
153 Clinically, patients have reported the insidious onset of cough, dyspnea, and low-grade fever. In some
154 cases, however, onset of symptoms may be acute. Pulmonary function studies have revealed
155 diminished diffusion capacity and decreased pulmonary compliance. It is important to exclude more
156 common conditions (such as opportunistic infections or leukemic infiltration of the lungs) with
157 appropriate diagnostic techniques. If measures such as sputum cultures, virologic studies, and
158 exfoliative cytology fail to establish an etiology for the pulmonary infiltrates, lung biopsy may be
159 necessary to establish the diagnosis. Treatment of established busulfan-induced pulmonary fibrosis is
160 unsatisfactory; in most cases the patients have died within 6 months after the diagnosis was
161 established. There is no specific therapy for this complication. MYLERAN should be discontinued if
162 this lung toxicity develops. The administration of corticosteroids has been suggested, but the results
163 have not been impressive or uniformly successful.

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

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

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

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

180 Ovarian suppression and amenorrhea with menopausal symptoms commonly occur during busulfan
181 therapy in premenopausal patients. Busulfan has been associated with ovarian failure including
182 failure to achieve puberty in females. Busulfan interferes with spermatogenesis in experimental

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183 animals, and there have been clinical reports of sterility, azoospermia, and testicular atrophy in male
184 patients.

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

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

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

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

213

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214 PRECAUTIONS

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

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

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

241 **Laboratory Tests:** It is recommended that evaluation of the hemoglobin or hematocrit, total white
242 blood cell count and differential count, and quantitative platelet count be obtained weekly while the
243 patient is on busulfan therapy. In cases where the cause of fluctuation in the formed elements of the

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

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

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

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

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

268 Busulfan clearance may be reduced in the presence of cyclophosphamide (see CLINICAL
269 PHARMACOLOGY).

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

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

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

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

282 **Pediatric Use:** See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION
283 sections.

284

285 **ADVERSE REACTIONS**

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

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

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

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

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

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

305 **Dermatologic:** Hyperpigmentation is the most common adverse skin reaction and occurs in 5% to
306 10% of patients, particularly those with a dark complexion.

307 **Metabolic:** In a few cases, a clinical syndrome closely resembling adrenal insufficiency and
308 characterized by weakness, severe fatigue, anorexia, weight loss, nausea and vomiting, and
309 melanoderma has developed after prolonged busulfan therapy. The symptoms have sometimes been
310 reversible when busulfan was withdrawn. Adrenal responsiveness to exogenously administered
311 ACTH has usually been normal. However, pituitary function testing with metyrapone revealed a
312 blunted urinary 17-hydroxycorticosteroid excretion in 2 patients. Following the discontinuation of
313 busulfan (which was associated with clinical improvement), rechallenge with metyrapone revealed
314 normal pituitary-adrenal function.

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

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

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

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

330 **Observed During Clinical Practice:** The following events have been identified during post-
331 approval use of busulfan. Because they are reported voluntarily from a population of unknown size,

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332 estimates of frequency cannot be made. These events have been chosen for inclusion due to a
333 combination of their seriousness, frequency of reporting, or potential causal connection to busulfan.

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

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

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

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

339 **Respiratory:** Pneumonia.

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

342

343 OVERDOSAGE

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

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

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

360

361 DOSAGE AND ADMINISTRATION

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

368 A decrease in the leukocyte count is not usually seen during the first 10 to 15 days of treatment; the
369 leukocyte count may actually increase during this period and it should not be interpreted as resistance
370 to the drug, nor should the dose be increased. Since the leukocyte count may continue to fall for more
371 than 1 month after discontinuing the drug, it is important that busulfan be discontinued *prior* to the
372 total leukocyte count falling into the normal range. When the total leukocyte count has declined to
373 approximately 15,000/mcL, the drug should be withheld.

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

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

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

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

386

387 **HOW SUPPLIED**

388 MYLERAN is supplied as white, film-coated, round, biconvex tablets containing 2 mg busulfan in
389 amber glass bottles with child-resistant closures. One side is imprinted with "GX EF3" and the other
390 side is imprinted with an "M."

391 Bottle of 25 (NDC 0173-0713 -25)

392 Bottle of 100 (NDC 0173-0713-XX)

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393 **Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled**
394 **Room Temperature).**

395

396

397 **REFERENCES**

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