

# Prescribing Information

**Pr MYLERAN<sup>®</sup>**

**Busulfan Tablets BP**

**2 mg**

**Antileukemic**

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## Prescribing Information

**PrMYLERAN<sup>®</sup>**

**Busulfan Tablets BP  
2 mg**

**Antileukemic**

### Caution

**MYLERAN<sup>®</sup> (busulfan) is a potent cytotoxic drug and should be used only by physicians experienced in the administration of cancer chemotherapeutic drugs. Blood counts should be taken at frequent intervals but minimally once weekly. Therapy should be discontinued or the dosage reduced at the first signs of abnormal depression of bone marrow.**

### Clinical Pharmacology

MYLERAN<sup>®</sup> (busulfan) is a bifunctional alkylating agent. Binding to DNA is believed to play a role in its mode of action, and di-guanyl derivatives have been isolated, but interstrand crosslinking has not been conclusively demonstrated.

The basis for the uniquely selective effect of busulfan on granulocytopenia is not fully understood.

Early pharmacokinetic studies were carried out with radioactively labelled busulfan. More recently, gas liquid chromatography with selected ion monitoring has been used to quantitate busulfan in biological fluids. Absorption of busulfan shows intraindividual variation. Both zero and first-order absorption, one compartment open models have been fitted to pharmacokinetic data. The mean half-life for drug elimination was 2.57 hours.

More recently, automated solid phase extraction with liquid chromatography mass spectrometry analysis has been used to quantitate busulfan in plasma. In a study of 12 patients administered single oral dose of busulfan 4 to 8 mg, the mean (dose adjusted to 4mg) maximum plasma

concentration ( $68 \pm 24\text{ng/ml}$ ) occurred between 0.5 and 2 hours after administration. The mean terminal plasma elimination half-life was  $2.7 \pm 0.5$  hours.

The bioavailability of oral busulfan shows large intraindividual variation ranging from 22% to 120% in adults and children.

The pharmacokinetics of busulfan have also been studied in patients following high-dose administration (1 mg/kg administered orally every 6 hours for 4 days). The mean elimination half-life was 2.3 hours after the final busulfan dose, but 3.4 hours after the first dose. The mean steady-state plasma concentration was 1.1 microgram/mL after 2 to 3 doses 6 hours apart. Due to the variable absorption kinetics observed, it was not possible to evaluate the order of kinetics.

The primary mode of elimination of busulfan is through extensive metabolism and very little (1-2%) of the drug is excreted unchanged in the urine. In humans, busulfan is at least partly metabolized via the glutathione route. The urinary metabolites of busulfan have been identified as 3- hydroxysulpholane, tetrahydrothiophene 1-oxide and sulpholane, in patients treated with high-dose busulfan. The clinical activity of these compounds, however, remains unclear.

Busulfan given in high doses has recently been shown to enter the cerebrospinal fluid (CSF) in concentrations comparable to those found in plasma, with a mean CSF:plasma ratio of 1.3 : 1. The saliva:plasma distribution of busulfan was 1.1 : 1.

The level of busulfan bound reversibly to plasma proteins has been variably reported to range from insignificant to approximately 55%. Irreversible binding of drug to blood cells and plasma proteins has been reported to be 47% and 32%, respectively.

## **Indications and Clinical Use**

Chronic granulocytic (myelocytic, myeloid) leukemia for the production of remissions. May be used with extreme caution in patients with prior radiation or  $P_{32}$  therapy and in those untreated by any other means.

## **Contraindications**

Busulfan should not be given if neutrophil or platelet counts are depressed.

MYLERAN® (busulfan) should not be used in patients whose disease has demonstrated resistance to busulfan. Busulfan should not be given to patients with previous hypersensitivity reaction to the drug or any of its components.

## Warnings

**Caution: Busulfan is a potent cytotoxic drug. Blood counts should be taken at frequent intervals and not less than weekly. Therapy should be discontinued or the dosage reduced at the first signs of abnormal depression of bone marrow.**

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

A rare, important complication of busulfan therapy is the development of bronchopulmonary dysplasia with pulmonary fibrosis. Symptoms have been reported to occur within 8 months to 10 years after initiation of therapy - the average duration of therapy being 4 years. The histologic findings associated with busulfan lung mimic those seen following pulmonary irradiation. Clinically, patients have reported the insidious onset of cough, dyspnea, and low-grade fever. Pulmonary function studies have revealed diminished diffusion capacity and decreased pulmonary compliance. It is important to exclude more common conditions (such as opportunistic infections or leukemic infiltration of the lungs) with appropriate diagnostic techniques. If measures such as sputum cultures, virologic studies and exfoliative cytology fail to establish an etiology for the pulmonary infiltrates, lung biopsy may be necessary to establish the diagnosis. Treatment of established busulfan-induced pulmonary fibrosis is unsatisfactory; in most cases the patients have died within 6 months after the diagnosis was established. There is no specific therapy for this complication other than the immediate discontinuation of

busulfan. The administration of corticosteroids has been suggested, but the results have not been impressive or uniformly successful.

If anaesthesia is required in patients with possible pulmonary toxicity, the concentration of inspired oxygen should be kept as low as safely possible and careful attention given to post-operative respiratory care.

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

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

Busulfan is mutagenic in mice and, possibly in man.

A number of malignant tumours have been reported in patients on busulfan therapy and this drug may be a human carcinogen. Four cases of acute leukemia occurred among 243 patients treated with busulfan as adjuvant chemotherapy following surgical resection of bronchogenic carcinoma. All four cases were from a subgroup of 19 of these 243 patients who developed pancytopenia while taking busulfan five to eight years before leukemia became clinically apparent. These findings suggest that busulfan is leukemogenic, although its mode of action is uncertain.

Hepatic veno-occlusive disease, which may be life-threatening, has been reported following the investigational use of very high doses of busulfan in combination with cyclophosphamide or other chemotherapeutic agents prior to bone marrow transplantation. Possible risk factors for the development of hepatic veno-occlusive disease include: total busulfan dose exceeding 16 mg/kg based on the ideal body weight, and concurrent use of multiple alkylating agents.

A clear cause and effect relationship with busulfan has not been demonstrated. Periodic measurement of serum transaminases, alkaline phosphatase, and bilirubin is indicated for early detection of hepatotoxicity. A reduced incidence of hepatic veno-occlusive disease and other

regimen-related toxicities have been observed in patients treated with high-dose MYLERAN® (busulfan) and cyclophosphamide when the first dose of cyclophosphamide has been delayed for > 24 hours after the last dose of busulfan.

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

If high-dose busulfan is prescribed, patients should be given prophylactic anticonvulsant therapy preferably with a benzodiazepine rather than enzyme inducing anticonvulsants (eg. phenytoin) (see Drug Interactions).

Patients co-prescribed systemic itraconazole with busulfan should be monitored for signs of busulfan toxicity (see Drug Interactions).

### **Use in Pregnancy**

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be used when either partner is receiving busulfan.

Busulfan may cause fetal harm when administered to a pregnant woman. Although there have been a number of cases reported where apparently normal children have been born after busulfan treatment during pregnancy, one case has been cited where a malformed baby was delivered by a mother treated with busulfan. During the pregnancy that resulted in the malformed infant, the mother received x-ray therapy early in the first trimester, mercaptopurine until the third month, then busulfan until delivery.

When cytotoxic drugs are used in pregnancy, the possible teratogenic effect on the fetus should be kept in mind. Delay treatment as long as possible and certainly until after the first 3 months of pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant. In every individual case the expected benefit of treatment to the mother must be weighed against the possible risks to the fetus.

There is evidence from animal studies that busulfan produces foetal abnormalities and adverse effects on off-spring, including defects of the musculo-skeletal system, reduced body weight and size, and impairment of gonadal development and effects on fertility.

In pregnant rats, busulfan produces sterility in both male and female offspring due to the absence of germinal cells in testes and ovaries. Germinal cell aplasia or sterility in offspring of mothers receiving busulfan during pregnancy has not been reported in humans.

### **Effects on Fertility**

Ovarian suppression and amenorrhea with menopausal symptoms commonly occur during busulfan therapy in premenopausal patients. In very rare cases, recovery of ovarian failure has been reported with continuing treatment. Treatment with high-dose MYLERAN® has been associated with severe and persistent ovarian failure including failure to achieve puberty after administration to young girls and pre-adolescents. Busulfan interferes with spermatogenesis in experimental animals and there have been clinical reports of sterility, azoospermia and testicular atrophy in male patients.

## **Precautions**

### **General**

Use of MYLERAN® (busulfan) should be restricted to patients for whom complete blood counts are available at intervals of at least 1 week. The most careful hematological control is essential since large doses may produce irreversible depression of the bone marrow which may not be obvious for 4 to 6 months.

The most consistent, dose-related toxicity is bone marrow suppression. This may be manifested by anemia, leukopenia, thrombocytopenia or any combination of these. It is imperative that patients be instructed to report promptly the development of fever, sore throat, signs of local infection, bleeding from any site or symptoms suggestive of anemia. Any one of these findings may indicate busulfan toxicity; however, they may also indicate transformation of the disease to an acute “blastic” form. Since busulfan may have a delayed effect on the bone marrow, it is important to withdraw the medication temporarily at the first sign of an abnormally large or exceptionally rapid fall in any of the formed elements of the blood.

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

### **Use in Pregnancy**

Teratogenic Effects: see WARNINGS

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

### **Use in Lactation**

It is not known whether busulfan or its metabolites are excreted in human milk. Mothers receiving MYLERAN® should not breast feed their infants. Because of the potential for tumorigenicity shown in animal and human studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### **Drug Interactions**

Busulfan may cause additive pulmonary toxicity when administered with other cytotoxic drugs.

Busulfan may cause additive myelosuppression when used with other myelosuppressive drugs.

The administration of phenytoin to patients receiving high-dose busulfan may result in a decrease in the myeloblastic effect due to increased busulfan clearance.

In one study, 12 of approximately 330 patients receiving continuous busulfan and thioguanine therapy for treatment of chronic myelogenous leukemia were found to have esophageal varices associated with abnormal liver function tests. Subsequent liver biopsies were performed in four of these patients, all of which showed evidence of nodular regenerative hyperplasia. Duration of combination therapy prior to the appearance of esophageal varices ranged from 6 to 45 months. However, subsequent large clinical trials have demonstrated increasing evidence that thioguanine alone results in severe liver toxicity, negating the influence of busulphan.

The concomitant systemic administration of itraconazole to patients receiving high-dose busulfan may result in reduced busulfan clearance.

A reduced incidence of hepatic veno-occlusive disease and other regimen-related toxicities have been observed in patients treated with high-dose MYLERAN® and cyclophosphamide when the first dose of cyclophosphamide has been delayed for > 24 hours after the last dose of busulfan.

## **Laboratory Tests**

It is recommended that evaluation of the hemoglobin or hematocrit, total white blood cell count and differential count, and quantitative platelet count be obtained weekly while the patient is on busulfan therapy. In cases where the cause of fluctuation in the formed elements of the peripheral blood is obscure, bone marrow examination may be useful for evaluation of marrow status. A decision to increase, decrease, continue, or discontinue a given dose of busulfan should be based not only on the absolute hematologic values, but also on the rapidity with which changes are occurring. The dosage of busulfan may need to be reduced if combined with other drugs whose primary toxicity is myelosuppression. Occasionally patients may be unusually sensitive to busulfan administered at standard dosages and suffer neutropenia or thrombocytopenia after a relatively short exposure to the drug. Busulfan should not be used where facilities for complete blood counts, including quantitative platelet counts, are not available at weekly (or more frequent) intervals.

## **Information for Patients**

Patients beginning therapy with busulfan should be informed of the importance of having periodic blood counts and to immediately report any unusual fever or bleeding. Aside from the major toxicity of myelosuppression, patients should be instructed to report any difficulty in breathing, persistent cough or congestion. They should be told that diffuse pulmonary fibrosis is an infrequent but serious and potentially life-threatening complication of long-term busulfan therapy. Patients should be alerted to report any signs of abrupt weakness, unusual fatigue, anorexia, weight loss, nausea and vomiting, and melanoderma that could be associated with a syndrome resembling adrenal insufficiency. Patients should never be allowed to take the drug without medical supervision and they should be informed that other encountered toxicities to busulfan include infertility, amenorrhea, skin hyperpigmentation, drug hypersensitivity, dryness of the mucous membranes and rarely cataract formation. Patients of childbearing potential should be advised to avoid becoming pregnant. Mothers receiving MYLERAN® should not breast feed their infants. The increased risk of a secondary malignancy should be explained to the patient.

## **Adverse Reactions**

### **Hematologic**

The chief toxic effect is a dosage-related myelosuppression which may cause leucopenia and thrombocytopenia (hemorrhage) and eventually lead to pancytopenia.

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

### **Pulmonary**

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

The lung pathology may be complicated by superimposed infections.

Pulmonary ossification and dystrophic calcification have also been reported.

### **Metabolic**

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

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

### **Cardiac**

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

One case of endocardial fibrosis has been reported in a 79 year old woman who received a total dose of 7200 mg over a period of nine years for the management of chronic myelogenous leukemia. At autopsy, she was found to have endocardial fibrosis of the left ventricle in addition to interstitial pulmonary fibrosis.

### **Ocular**

Busulfan is capable of inducing cataracts in rats and there have been several reports indicating that this is a rare complication in humans. In the few cases reported in humans, cataracts have occurred only after prolonged administration of busulfan.

Corneal thinning has been reported with the investigational use of high-dose MYLERAN® prior to bone marrow transplantation.

### **Dermatologic**

Esophageal varices have been reported in patients receiving continuous busulfan and thioguanine therapy for treatment of chronic myelogenous leukemia (see PRECAUTIONS, Drug Interactions).

Hyperpigmentation is the most common adverse skin reaction and occurs in 5% to 10% of patients, particularly those with a dark complexion. It is often most marked on the neck, upper trunk, nipples, abdomen and palmar creases.

### **Gastrointestinal and Hepatic**

Hyperbilirubinemia, jaundice and hepatic veno-occlusive disease and centrilobular sinusoidal fibrosis with hepatocellular atrophy and necrosis have been observed in patients receiving high-dose busulfan (see WARNINGS).

### **Miscellaneous**

Other complications of therapy include instances of nausea, vomiting, diarrhea, dryness of the oral mucous membranes and cheilosis, glossitis, urticaria, erythema multiform, erythema nodosum, porphyria cutanea tarda, myasthenia gravis, cholestatic jaundice, impotence, sterility, amenorrhea, gynecomastia, excessive dryness and fragility of the skin with anhidrosis, alopecia and, hemorrhagic cystitis. Seizures have been observed in patients receiving higher than recommended doses of busulfan (see PRECAUTIONS, General).

## **Symptoms and Treatment of Overdosage**

There is no known antidote to busulfan. The acute dose-limiting toxicity of MYLERAN® (busulfan) in man is myelosuppression. The main effect of chronic overdosage is bone marrow depression and pancytopenia. Survival after a single dose of 140 mg has been reported in an 18 kg 4 year old child, but hematological toxicity is likely to be more profound with chronic overdosage. If high dose MYLERAN® is used in association with bone marrow transplantation, gastrointestinal toxicity becomes dose limiting with mucositis, nausea, vomiting, diarrhea and anorexia.

Symptoms: Purpuric hemorrhages.

Treatment: The hematologic status should be closely monitored and vigorous supportive measures instituted if necessary. Induction of vomiting or gastric lavage followed by administration of charcoal would be indicated if ingestion were recent. Dialysis should be considered in the management of overdose as there is one report of successful dialysis of busulfan.

If high-dose MYLERAN® is used in association with bone marrow transplantation, gastrointestinal toxicity becomes dose limiting with mucositis, nausea, vomiting, diarrhea and anorexia.

## **Dosage and Administration**

Busulfan is administered orally at a dosage of 0.06 mg/kg (1.8 mg/m<sup>2</sup> body surface area) to a total maximum dose of 4 mg daily, until maximum hematological and clinical improvement is obtained or symptoms of toxicity supervene. During remission the patient is examined at monthly intervals and the treatment is resumed when the white cell count reaches

50,000/mm<sup>3</sup>. When remission is shorter than 3 months, maintenance therapy of 1 to 3 mg daily may be advisable in order to keep the hematological status under control and prevent rapid relapse. Discontinue drug or reduce dosage at the first sign of abnormal depression of platelets, hemoglobin, or low white blood cell count.

## Pharmaceutical Information

### Drug Substance

<u>Proper Name:</u>	Busulfan
<u>Chemical Name:</u>	1,4-Butanediol, dimethanesulfonate
<u>Structural Formula:</u>	$\text{CH}_3\text{SO}_2\text{O}(\text{CH}_2)_4\text{OSO}_2\text{CH}_3$
<u>Molecular Formula:</u>	$\text{C}_6\text{H}_{14}\text{O}_6\text{S}_2$
<u>Molecular Weight:</u>	246.31
<u>Description:</u>	White or almost white crystalline powder. Very slightly soluble in water, alcohol and in ether; freely soluble in acetone and in chloroform.

### Composition

MYLERAN® Tablets contain 2 mg busulfan and the non-medicinal ingredients, anhydrous lactose, magnesium stearate, and pregelatinized starch. The film coat contains hypromellose (hydroxypropyl methylcellulose), titanium and triacetin.

### Stability and Storage Recommendations

MYLERAN® Tablets should be stored between 15° and 30°C.

### Special Instructions

All materials which have come in contact with cytotoxic drugs should be segregated and incinerated at 1000°C or more.

Tablets should be returned to the manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

Personnel regularly involved in the preparation and handling of cytotoxic agents should have bi-annual blood examinations.

Care should be taken when handling or halving the tablets so as not to contaminate hands or to inhale the drug.

### **Availability of Dosage Forms**

MYLERAN® Tablets are white, film-coated, round, biconvex tablets engraved "GX EF3" on one side and "M" on the other. Bottles of 25.

## Bibliography

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3. Shepard PC, Fooks J, Gray R, Allan NC. Thioguanine used in maintenance therapy of chronic myeloid leukemia causes non-cirrhotic portal hypertension. Results from MRC CML II Trial comparing busulphan with busulphan and thioguanine. *BR J Haematol* 1991; 79: 185 - 192.