PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrMYLERAN®

Busulfan

Tablets 2 mg, Oral

Manufacturer's Standard

Antileukemic

ATC code L01AB01.

Aspen Pharmacare Canada Inc.
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Date of Initial Approval:
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MYLERAN® (busulfan) is indicated for:
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.

1.1 Pediatrics

Pediatrics (**0-18 years)**: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ *65* years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

MYLERAN® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

- MYLERAN® should not be given if neutrophil or platelet counts are depressed.
- MYLERAN® should not be used in patients whose disease has demonstrated resistance to busulfan.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

MYLERAN® (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. Events of irreversible bone marrow aplasia have been reported.
See section 7 for additional information on warnings and precautions.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Health Canada has not authorized an indication for pediatric use.

4.2 Recommended Dose and Dosage Adjustment

Induction in adults:. MYLERAN® is administered orally at a dosage of 0.06 mg/kg (1.8 mg/m^2 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^3. 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.

5 OVERDOSAGE

There is no known antidote to MYLERAN®. The acute dose-limiting toxicity of MYLERAN® 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 MYLERAN®.

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets 2 mg	Tablet core: anhydrous lactose, magnesium stearate, and pregelatinized starch. Tablet coating: The film coat contains hypromellose (hydroxypropyl methylcellulose), titanium dioxide and triacetin.

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.

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.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

Carcinogenesis and Mutagenesis

MYLERAN® 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 MYLERAN® therapy, chromosome aberrations have been reported in cells from patients receiving MYLERAN®.

MYLERAN® is mutagenic in mice and, possibly in man.

A number of malignant tumours have been reported in patients on MYLERAN® therapy and this drug may be a human carcinogen. Four cases of acute leukemia occurred among 243 patients treated with MYLERAN® 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 MYLERAN® five to eight years before leukemia became clinically apparent. These findings suggest that MYLERAN® is leukemogenic, although its mode of action is uncertain.

Cardiovascular

Cardiac tamponade has been reported in a small number of patients with thalassemia (2% in one series) who received high doses of MYLERAN® 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 MYLERAN® 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 MYLERAN® should be monitored for signs of busulfan toxicity (see Drug Interactions).

Fertility

MYLERAN® can lead to suppression of ovarian function and amenorrhoea in women and suppression of spermatogenesis in men. Ovarian suppression and amenorrhea with menopausal symptoms commonly occur during MYLERAN® 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. MYLERAN® interferes with spermatogenesis in experimental animals and there have been clinical reports of sterility, azoospermia and testicular atrophy in male patients.

MYLERAN® interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Men treated with MYLERAN® should be informed about sperm preservation prior to treatment (*see Fertility and Adverse Reactions*).

Hematologic

Use of MYLERAN® 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. Events of irreversible bone marrow aplasia have been reported.

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 MYLERAN® 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.

The most frequent, serious side effect of treatment with MYLERAN® is the induction of bone marrow failure (which may or may not be anatomically hypoplastic) resulting in severe pancytopenia. The pancytopenia caused by MYLERAN® 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. **MYLERAN® 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.

Hepatic/Biliary/Pancreatic

MYLERAN® has not been studied in patients with hepatic impairment. Since busulfan is mainly metabolized through the liver, caution should be observed when MYLERAN® is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment.

Hepatic veno-occlusive disease, which may be life-threatening, has been reported following the investigational use of very high doses of MYLERAN® 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 MYLERAN® dose exceeding 16 mg/kg based on the ideal body weight, and concurrent use of multiple alkylating agents.

Hepatic veno-occlusive disease is a major complication that can occur during treatment with MYLERAN® Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or prior progenitor cell transplant may be at an increased risk (*see Adverse Reactions section*).

A clear cause and effect relationship with MYLERAN® 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® and cyclophosphamide when the first dose of cyclophosphamide has been delayed for > 24 hours after the last dose of MYLERAN®.

Immune

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.

Monitoring and 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 MYLERAN® 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 MYLERAN® should be based not only on the absolute hematologic values, but also on the rapidity with

which changes are occurring. The dosage of MYLERAN® may need to be reduced if combined with other drugs whose primary toxicity is myelosuppression. Occasionally patients may be unusually sensitive to MYLERAN® administered at standard dosages and suffer neutropenia or thrombocytopenia after a relatively short exposure to the drug. MYLERAN® should not be used where facilities for complete blood counts, including quantitative platelet counts, are not available at weekly (or more frequent) intervals.

Careful attention must be paid to monitoring the blood counts throughout treatment to avoid the possibility of excessive myelosuppression and the risk of irreversible bone marrow aplasia *(see ADVERSE REACTIONS* section*).*

Patients co-administered itraconazole or metronidazole with conventional dose MYLERAN® should be monitored closely for signs of busulfan toxicity. Weekly measurements of blood counts are recommended when co-administering these drugs *(*see *DRUG INTERACTIONS* section*)*.

Nervous system disorders

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

Renal

As studies in renally impaired patients have not been conducted, dose modification is not recommended in these patients MYLERAN® (busulfan) is moderately excreted in the urine and excreted intact at ≤1%. However, caution is recommended. (See ADVERSE REACTIONS, Renal and urinary disorders).

Respiratory

A rare, important complication of MYLERAN® 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 MYLERAN® 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 MYLERAN®-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 MYLERAN®. 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.

MYLERAN® should be discontinued if lung toxicity develops *(see ADVERSE REACTIONS section)*

7.1 Special Populations

7.1.1 Pregnant Women

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

MYLERAN® 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 MYLERAN® treatment during pregnancy, one case has been cited where a malformed baby was delivered by a mother treated with MYLERAN®**.** 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 MYLERAN® 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.

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.

7.1.2 Breast-feeding

It is not known whether MYLERAN® 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.

7.1.3 Pediatrics

Pediatrics (0-18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following table of adverse reactions originated from the use of MYLERAN® or busulfan in combination with other therapeutic agents.

Table 2.

System organ class	Frequency	Side effects
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Leukaemia secondary to oncology chemotherapy (see Warnings and Precautions; Carcinogenicity)

Blood and lymphatic system disorders *	Very common	Dose-related bone marrow failure, manifesting as leukopenia and particularly thrombocytopenia
	Rare	Aplastic anaemia
	Unknown	Pancytopenia
Immune System Disorders	Rare	Sjögren's syndrome
Nervous system disorders *	Rare	At high-dose: seizure (see Interactions and Warnings and Precautions)
	Very rare	Myasthenia gravis
Eye disorders *	Rare	Lens disorder and cataract (which may be bilateral) corneal thinning (reported after bone marrow transplantation preceded by high-dose MYLERAN® treatment)
Cardiac disorders *	Common	At high-dose: cardiac tamponade in patients with thalassaemia
	Unknown	Endocardial fibrosis
Respiratory, thoracic and mediastinal disorders *	Very common	At high-dose: idiopathic pneumonia syndrome
	Common	Interstitial lung disease following long term conventional dose use
	Rare	Interstitial pulmonary fibrosis
Metabolism and nutritional disorders *	Common	Hyperuricemia and/or hyperuricosuria, uric acid nephropathy
Gastrointestinal disorders *	Very common	At high-dose: nausea, vomiting, diarrhoea, mouth ulceration
	Rare	At conventional dose: nausea, vomiting, diarrhoea, mouth ulceration, which may possibly be ameliorated by using divided doses. Dry mouth
	Unknown	Glossitis
Hepatobiliary disorders *	Very common	At high-dose: hyperbilirubinaemia, jaundice, veno occlusive liver disease (see Warnings and Precautions and Interactions) and biliary fibrosis with hepatic atrophy and hepatic necrosis
	Rare	Cholestatic jaundice and hepatic function abnormal, at

		conventional dose. Biliary fibrosis
	Unknown	Centrilobular sinusoidal fibrosis
Skin and subcutaneous tissue disorders *	Common	Alopecia at high-dose. Skin hyperpigmentation (see also General disorders and administration site conditions)
	Rare	Alopecia at conventional dose, skin reactions including urticaria, erythema multiforme, erythema nodosum, porphyria non-acute, rash, dry skin and skin fragility with complete anhydrosis cheilosis
	Unknown	Esophageal varices
Injury, poisoning and procedural complications	Rare	Radiation skin injury is increased in patients receiving radiotherapy soon after high-dose MYLERAN®
Renal and urinary disorders *	Common	At high-dose[1)2)]: cystitis haemorrhagic in combination with cyclophosphamide
Reproductive system and breast disorders *	Very common	Ovarian disorder and amenorrhoea with menopausal symptoms in pre-menopausal patients at high-dose; severe and persistent ovarian failure, including pubertal failure after administration to young girls and pre-adolescents at high-dose. Male sterility, azoospermia and testicular atrophy in male patients receiving MYLERAN®
	Uncommon	Ovarian disorder and amenorrhoea with menopausal symptoms in pre-menopausal patients at conventional dose.
	Very rare	Gynaecomastia
	Unknown	Impotence
General disorders and administration site conditions *	Rare	Dysplasia

[1)] Induction 0.06 mg/kg/day with an initial daily maximum of 4 mg.

[2)] Maintenance is on average 0.5 to 2 mg daily.

*Description of selected adverse events

Blood and lymphatic system disordersThe 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®.

Events of irreversible bone marrow aplasia have been reported.

Nervous system disorders

Seizures have been observed in patients receiving higher than recommended doses of MYLERAN®.

Other complications of therapy include myasthenia gravis

Respiratory, thoracic and mediastinal disorders

Pulmonary toxicity after either high or conventional dose treatment typically presents with non-specific non-productive cough, dyspnoea and hypoxia with evidence of abnormal pulmonary physiology. Other cytotoxic agents and radiotherapy may cause additive lung toxicity (see Interactions). It is possible that subsequent radiotherapy can augment subclinical lung injury caused by busulphan**.** Once pulmonary toxicity is established the prognosis is poor despite busulphan withdrawal and there is little evidence that corticosteroids are helpful. Idiopathic pneumonia syndrome is a non-infectious diffuse pneumonia which usually occurs within three months of high dose busulphan conditioning prior to allogeneic or autologous haemopoietic transplant. Diffuse alveolar haemorrhage may also be detected in some cases after broncholavage. Chest X-rays or CT scans show diffuse or non- specific focal infiltrates and biopsy shows interstitial pneumonitis and diffase alveolar damage and sometimes fibrosis. Interstitial pneumonitis may occur following conventional dose use and lead to pulmonary fibrosis. This usually occurs after prolonged treatment over a number of years. The onset is usually insidious but may also be acute. Histological features include atypical changes of the alveolar and bronchiolar epithelium and the presence of giant cells with large hyperchromatic nuclei.

The lung pathology may be complicated by superimposed infections. Pulmonary ossification and dystrophic calcification have also been reported.

Metabolism and nutrition disorders

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 MYLERAN® therapy. The symptoms have sometimes been reversible when MYLERAN® 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 MYLERAN® (which was associated with clinical improvement), rechallenge with metyrapone revealed normal pituitary-adrenal function.

Cardiac disorders

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.

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.

Eye Disorders

MYLERAN® 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 MYLERAN®.

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

Skin and subcutaneous disorders

Esophageal varices have been reported in patients receiving continuous busulfan and thioguanine therapy for treatment of chronic myelogenous leukemia.

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 (see *Adverse Reactions, Metabolic* section).

Other complications of therapy include urticaria, excessive dryness and fragility of the skin with anhidrosis, alopecia, erythema multiform, erythema nodosum and porphyria cutanea tarda,

Renal and urinary disorders

Hemorrhagic cystitis.

Gastrointestinal disorders

Other complications of therapy include instances of nausea, vomiting, diarrhea, dryness of the oral mucous membranes, cheilosis, and glossitis.

Hepatobiliary disorders

Hyperbilirubinemia, jaundice,veno-occlusive liver disease and biliary fibrosis with hepatic atrophy and necrosis have been observed in patients receiving high-dose MYLERAN®. Retrospective review of post mortem reports of patients who had been treated with low-dose MYLERAN® for at least two years for chronic myeloid leukaemia showed evidence of centrilobular sinusoidal fibrosis (see **WARNINGS AND PRECAUTIONS).**

Other complications of therapy include instances of cholestatic jaundice.

Reproductive system and breast disorders

Other complications of therapy include instances of impotence, sterility, amenorrhea, and gynecomastia.

Studies of busulfan treatment in animals have shown reproductive toxicity (see *NON- CLINICAL INFORMATION* section).

In very rare cases, recovery of ovarian function has been reported with continuing treatment. See **WARNINGS AND PRECAUTIONS, Fertility and Special Populations, Pregnant Women**.

General disorders and administration site conditions

Many histological and cytological changes have been observed in patients treated with MYLERAN®, including widespread dysplasia affecting uterine cervical, bronchial and other epithelia. Most reports relate to long-term treatment but transient epithelial abnormalities have been observed following short-term, high dose treatment.

9 DRUG INTERACTIONS

9.1 Overview

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

MYLERAN® may cause additive myelosuppression when used with other myelosuppressive drugs.

The administration of phenytoin to patients receiving high-dose MYLERAN® may result in a decrease in the myeloblative 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 MYLERAN® may result in reduced busulfan clearance. Metronidazole has been reported to increase trough levels of busulfan by approximately 80%. Fluconazole had no effect on busulfan clearance. Consequently, high-dose MYLERAN® in combination with itraconazole or metronidazole is reported to be associated with an increased risk of busulfan toxicity.

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 MYLERAN®.

Paracetamol is described to decrease glutathione levels in blood and tissues, and may therefore decrease busulfan clearance when used in combination.

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see Warnings and Precautions).

9.2 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 - Established or Potential Drug-Drug Interactions

<Proper/Common name>	Source of Evidence	Effect	Clinical comment
Cyclophosphamide	T	hepatic veno-occlusive disease and other regimen-related toxicities	Caution is warranted for patients receiving high-dose MYLERAN®
Other cytotoxic drugs	T	additive pulmonary toxicity	Caution is warranted and therapeutic concentration monitoring is recommended

Itraconazole and metronidazole	C	reduced busulfan clearance	**Conventional dose treatment** Patients co-administered itraconazole or metronidazole with conventional dose MYLERAN® should be monitored closely for signs of MYLERAN® toxicity. Weekly measurements of blood counts are recommended when co-administering these drugs (see Interactions). **High Dose Treatment** Concomitant administration of itraconazole or metronidazole with high-dose MYLERAN® has been reported to be associated with an increased risk of MYLERAN® toxicity (see Interactions). Coadministration of metronidazole and high dose MYLERAN® is not recommended. Co-administration of itraconazole with high dose MYLERAN® should be at the discretion of the prescribing physician and should be based on a risk/benefit assessment
Paracetamol	T	decrease glutathione levels in blood and tissues	Caution is warranted and therapeutic concentration monitoring is recommended
phenytoin	T	decrease in the myeloblative effect due to increased busulfan clearance.	Caution is warranted for patients receiving high-dose MYLERAN®
thioguanine	C	esophageal varices associated with abnormal liver function tests; nodular regenerative hyperplasia	Caution is warranted and therapeutic concentration monitoring is recommended
Vaccination with live organism	C, T	potential to cause infection in immunocompromised hosts.	Vaccinations with live organism vaccines are not recommended in immunocompromised individuals

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

MYLERAN® 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 granulocytopoiesis is not fully understood.

10.2 Pharmacokinetics

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 ± 24ng/ml) occurred between 0.5 and 2 hours after administration. The mean terminal plasma elimination half-life was 2.7 ± 0.5 hours.

The bioavailability of oral busulfan shows large intraindividual variation ranging from 22% to 120% (mean 68%) 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.

Table 4 - Summary of busulfan Pharmacokinetic Parameters

	C_{max}	T_{max}	$t_{½}$ (h)	$AUC_{0-\infty}$	CL	Vd
Single dose mean (2 mg oral dose)	28 ± 5 nanograms/ ml	2hr	2.3 and 2.8h	125 ± 17 nanograms. h/ml	2.4 to 2.6 ml/min/kg	0.64 ± 0.12 L/kg

Absorption: The bioavailability of oral busulfan shows large intra-individual variation ranging from 47 % to 103 % (mean 80 %) in adults.

Distribution:

Busulfan given in high doses has 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 be insignificant or approximately 55%. Irreversible binding of drug to blood cells and plasma proteins has been reported to be 47 % and 32 %, respectively.

Metabolism:

Busulfan metabolism involves a reaction with glutathione, which occurs via the liver and is mediated by glutathione-S-transferase. The urinary metabolites of busulfan have been identified as 3-hydroxysulpholane, tetrahydrothiophene 1-oxide and sulpholane, in patients treated with high-dose busulfan.

Elimination:

. Very little (1 to 2 %) busulfan is excreted unchanged in the urine.

Special Populations and Conditions

Pediatrics: The bioavailability of oral busulfan shows large intra-individual variation ranging from 22 % to 120 % (mean 68 %) in children.

Plasma clearance is reported to be 2 to 4 times higher in children than in adults when receiving 1 mg/kg every 6 h for 4 days. Dosing children according to body surface area has been shown to give AUC and Cmax values similar to those seen in adults. The area under the curve has been shown to be half that of adults in children under the age of 15 years and a quarter of that of adults in children under 3 years of age.

Busulfan is reported to have a volume of distribution of 1.15 ± 0.52 L/kg in children.
When busulfan is administered at a dose of 1 mg/kg every 6 h for 4 days, the CSF:plasma ratio has been shown to be 1.02:1. However, when administered at a dose of 37.5 mg/m^2 every 6 h for 4 days the ratio was 1.39:1.

Obesity: Obesity has been reported to increase busulfan clearance. Dosing based on body surface area or adjusted ideal bodyweight should be considered in the obese.

11 STORAGE, STABILITY AND DISPOSAL

MYLERAN® Tablets should be stored between 15º and 30ºC.

12 SPECIAL HANDLING INSTRUCTIONS

All materials which have come in contact with cytotoxic drugs should be segregated and incinerated at 1000ºC 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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Busulfan

Chemical name: 1,4-Butanediol, dimethanesulfonate

Molecular formula and molecular mass: $C_6H_{14}O_6S_2$; 246.31

Structural formula: $CH_3SO_2O(CH_2)_4OSO_2CH_3$

Product Characteristics

White or almost white crystalline powder. Very slightly soluble in water, alcohol and in ether; freely soluble in acetone and in chloroform.

14 NON-CLINICAL TOXICOLOGY

Carcinogenesis, mutagenesis

Busulfan has been shown to be mutagenic in various experimental systems, including bacteria (Ames Salmonella test), fungi, Drosophila and cultured mouse lymphoma cells. In vivo cytogenetic studies in rodents have shown an increased incidence of chromosome aberrations in both germ cells and somatic cells after busulfan treatment.

Reproductive toxicology

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, impairment of gonadal development and effects on fertility.

Busulfan interferes with spermatogenesis in experimental animals. Limited studies in female animals indicate busulfan has a marked and irreversible effect on fertility via oocyte depletion.

References

1. Broxson EH, Wong R., Laya BF, Stork LC. Portal hypertension (PH) Very slightly solublein water, alcohol and in ether; freely soluble in acetone and in chloroform.

2. Key NS, Emerson PM, Allan NC, Kelly PMA, Chapman RWG, McGee Jo. Oesophageal varices associated with busulphan - thioguanine combination therapy for chronic myeloid leukemia. Lancet 1987; 2/8567: 1050 - 1052.

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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

MYLERAN®

busulfan tablets

Read this carefully before you start taking MYLERAN and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about MYLERAN.

Serious Warnings and Precautions

MYLERAN should only be prescribed by a healthcare professional experienced in the use of anti-cancer drugs.

Bone Marrow Suppression

Serious, irreversible bone marrow damage has been reported in people taking MYLERAN. Your healthcare professional will do blood tests at least once a week while you are taking MYLERAN. This will monitor the health of your bone marrow. If you experience any of the following symptoms while taking MYLERAN contact your healthcare professional immediately:

- symptoms of infections, including fever, chills, sore throat, mouth ulcers
- weakness, fatigue
- easy bruising, bleeding of the nose, gums or mouth, tiny red spots on the skin
- rash
- shortness of breath
- pale skin, lips and nail beds

What is MYLERAN used for?

- Myleran is used in adults to manage the symptoms of Chronic granulocytic (myelocytic, myeloid) leukemia and prevent it from getting worse. Chronic granulocytic (myelocytic, myeloid) leukemia is a cancer that starts in certain blood-forming cells found in the bone marrow.
- MYLERAN can be used in patients who have not had any other treatment for their cancer.
- MYLERAN can also be used in patients who have previously had their cancer treated with radiation or P_{32} therapy.

Use in Children

- MYLERAN should not be given to children.

How does MYLERAN work?

MYLERAN belongs to a group of anti-cancer medicines called alkylating agents. These medicines work by stopping cancer cells from growing and dividing.

What are the ingredients in MYLERAN?

Medicinal ingredients: busulfan

Non-medicinal ingredients: anhydrous lactose, hypromellose (hydroxypropyl methylcellulose), magnesium stearate, pregelatinized starch, titanium dioxide and triacetin.

MYLERAN comes in the following dosage forms:
Tablets, 2 mg

Do not use MYLERAN if:
- you are allergic (hypersensitive) to busulfan or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
- you have low neutrophil (a white blood cell) or platelet cell counts.
- your cancer has shown resistance to busulfan, the medicinal ingredient in MYLERAN.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MYLERAN. Talk about any health conditions or problems you may have, including if you:
- have low blood counts for red blood cells, white blood cells and/or platelet cells.
- have the blood disorder thalassemia.
- have had radiation or chemotherapy in the past or are recovering from recent chemotherapy.
- are receiving or have recently received live vaccines, such as oral polio, measles, mumps and rubella.
- have had a stem cell transplant.
- have chronic lung disease.
- have had or have a history of lung or breathing problems.
- have had seizures or head trauma or taken a medicine which can cause seizures.
- have or have had a history of kidney or liver problems.
- are breastfeeding or planning to breastfeed. You should not breastfeed while taking MYLERAN. Talk to your healthcare professional about the best way to feed your baby while you are being treated with MYLERAN.
- are pregnant or planning to become pregnant. You must not get pregnant while taking MYLERAN. If you think you might be pregnant contact your healthcare professional immediately.

Other warnings you should know about:

Birth Control for Men and Women
- Men and women must use effective birth control while taking MYLERAN.
- You must not get pregnant or father a child while taking MYLERAN. This is because MYLERAN may harm your/your female partner's unborn baby.
- Talk to your healthcare professional about the birth control methods that are right for you while you are taking MYLERAN.

Fertility in Men and Women
- MYLERAN can cause infertility in both women and men.
- This means you might not be able to get pregnant or father a child after you have finished taking MYLERAN.
- You should discuss ways to preserve your fertility with your healthcare professional before you start taking MYLERAN.
- Male patients should consider sperm preservation before they start taking MYLERAN.

Blood Tests
- Your healthcare professional will do weekly blood tests while you are taking MYLERAN.

- The blood tests will check for possible side effects and see how you are responding to MYLERAN.
- If you miss an appointment to have blood work done contact your healthcare professional immediately to reschedule.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MYLERAN:
- itraconazole and metronidazole, used to treat fungal infections
- other anti-cancer drugs and drugs that supress your immune system, such as thioguanine, cyclophosphamide
- paracetamol, used to treat pain and fever
- phenytoin, used to prevent seizures
- vaccines which contain live organisms such as oral polio, measles, mumps and rubella. MYLERAN can make your body less able to fight infections.

How to take MYLERAN:
- Your healthcare professional will tell you how to take MYLERAN. Always follow their instructions.
- Do not divide the tablets. Swallow them whole with water.

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Usual adult dose:
- Your healthcare professional will tell you how much MYLERAN to take and when to take it based on your height and body weight.
- Your healthcare professional may change your dose based on your blood test results and any side effects you are having.
- The maximum daily dose is 4 mg.

Overdose:

If you think you have taken too much MYLERAN, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take your dose of MYLERAN at your usual time, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Do not take a double dose to make up for a missed dose.

What are possible side effects from using MYLERAN?
These are not all the possible side effects you may feel when taking MYLERAN. If you experience any side effects not listed here, contact your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON **Low levels of white blood cells (leukopenia)**: fever, signs of infection (sore throat, sore mouth, painful urination, blood in the urine)			√
Low levels of blood platelets (thrombocytopenia): bleeding such as nose bleeds, bleeding gums and bruising easily			√
Pneumonia syndrome: pneumonia-like symptoms (such as fever, chills, dry cough, and breathing problems)		√	
Sexual problems: - In Women: reduced fertility, missed periods early menopause (irregular or no periods, vaginal dryness, hot flashes, chills, night sweats) - In Girls: delayed or absent puberty - In Boys and Men: delayed, reduced or stopped sperm production, reduction in testicle size		√	
Nausea, vomiting, diarrhea, mouth ulcers	√		
Liver problems: yellowing of the whites of the eyes or skin (jaundice), itchiness, dark urine, pale stool, increase in waist size, weight gain, abdominal swelling and pain, loss of appetite, shortness of breath		√	
COMMON **Heart problems**: anxiety and restlessness, low blood pressure (lightheadedness, dizziness and fainting, especially when you go from lying or sitting to standing), weakness, chest pain, trouble breathing, dizziness or loss of consciousness		√	

Secondary leukemia (another blood cancer different from the one you are taking MYLERAN to treat): tiredness, fever or night sweats, bone/joint pain, infection and bruising/bleeding.		√	
Inflammation of the lungs: breathlessness, cough, fever		√	
Alopecia: hair loss		√	
Skin colour changes: appearance of patches of dark skin particularly on the neck, upper trunk, nipples, abdomen and creases of the hands		√	
Bladder inflammation: blood in your urine, pain when passing urine		√	
RARE **Sjögren's syndrome:** two most common symptoms; dry eyes and a dry mouth. Other symptoms: joint pain and swelling, swollen salivary glands, skin rash or dry skin, vaginal dryness, prolonged tiredness		√	
Aplastic anemia (severe drop in red blood cells): tiredness, weakness, bruising, infections			√
Seizure or fits		√	
Cataracts or other eye problems: cloudy or blurry vision, colours seem faded, glare from lamps or headlights, double vision		√	
Skin injury after radiation	√		
Skin reactions: dry skin, rash, itchiness, lumps, blisters, fragile skin, cracked lips or corners of the mouth **Erythema nodosum:** reddish, painful, tender lumps most commonly located in the front of the legs below the knee		√	
Pulmonary fibrosis (scarred lung tissue): shortness of breath, especially during or after physical activity, coughing,		√	

lasting tiredness, chest discomfort, weight loss, mild fever			
VERY RARE **Myasthenia gravis:** weakness and rapid fatigue of any of the muscles under your voluntary control commonly leading to drooping eye lids and difficulty in speaking and swallowing or using your arms and legs		√	
Gynecomastia: enlargement of breast tissue in men		√	
UNKNOWN FREQUENCY **Bone marrow suppression:** infections (fever, chills, sore throat, mouth ulcers), weakness, fatigue, easy bruising, bleeding of the nose, gums or mouth, tiny red spots on the skin, rash, shortness of breath, pale skin, lips and nail beds.			√
Glossitis: swollen and inflamed tongue, problems talking, chewing, or swallowing, especially if you get sores on your tongue		√	
Endocardial fibrosis (thickening of the heart muscle): breathing difficulty, grunting sounds during breathing, coughing, irregular heart beat, chest pain		√	
Impotence: inability to have or maintain an erection	√		
Esophageal varices: blood in your vomit, black, tarry or bloody stools, lightheadedness		√	
Adrenal insufficiency: weakness, feeling very tired, weight loss, nausea, vomiting, dark skin patches		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

MYLERAN tablets should be stored between 15^{o} and 30^{o}C.

Keep out of reach and sight of children.

If you want more information about MYLERAN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website https://www.canada.ca/en/health-canada.html; the manufacturer's website http://www.aspenpharma.ca/, or by calling 1-844-330-1213

This leaflet was prepared by Aspen Pharmacare Canada Inc.

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