DATA SHEET

1. PRODUCT NAME (strength pharmaceutical form)
   MYLERAN™ (Busulfan Tablets 2mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   MYLERAN 2mg tablets are white, film-coated, round, biconvex tablets engraved “GX EF3” on one side and “M” on the other, supplied in amber glass bottles with a child resistant closure containing 100 tablets.

3. PHARMACEUTICAL FORM
   Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
   MYLERAN is indicated for the palliative treatment of the chronic phase of chronic granulocytic leukaemia.
   MYLERAN is effective in producing prolonged remission in polycythaemia vera, particularly in cases with marked thrombocytosis.
   MYLERAN may be useful in selected cases of essential thrombocythaemia and myelofibrosis.

4.2 Dose and method of administration
   General:

   MYLERAN tablets are usually given in courses or administered continuously. The dose must be adjusted for the individual patient under close clinical and haematological control. Should a patient require an average daily dose of less than the content of the available MYLERAN tablets, this can be achieved by introducing one or more busulfan free days between treatment days. The tablets should not be divided (see Instructions for Use/Handling).

   Obese patients

   Dosing based on body surface area or adjusted ideal body weight should be considered in the obese (see Pharmacokinetics)

   The relevant literature should be consulted for full details of treatment schedules.

   Chronic granulocytic leukaemia

   Induction in Adults:

   Treatment is usually initiated as soon as the condition is diagnosed.
The dose is 0.06mg/kg/day, with an initial daily maximum of 4mg, which may be given as a single dose.

There is individual variation in the response to MYLERAN and in a small proportion of patients the bone marrow may be extremely sensitive. (see Special Warnings and Special Precautions for Use).

The blood count must be monitored at least weekly during the induction phase and it may be helpful to plot counts on semi-log graph paper.

The dose should be increased only if the response is inadequate after three weeks.

Treatment should be continued until the total leucocyte count has fallen to between 15 and 25 x 10^9/L (typically 12 to 20 weeks). Treatment may then be interrupted, following which a further fall in the leucocyte count may occur over the next two weeks.

Continued treatment at the induction dose after this point or following depression of the platelet count to below 100 x 10^9/L is associated with a significant risk of prolonged and possibly irreversible bone marrow aplasia.

**Maintenance in Adults:**

Control of the leukaemia may be achieved for long periods without further MYLERAN treatment; further courses are usually given when the leucocyte count rises to 50 x 10^9/L, or symptoms return.

Some clinicians prefer to give continuous maintenance therapy. Continuous treatment is more practical when the duration of unmaintained remissions is short.

The aim is to maintain a leucocyte count of 10-15 x 10^9/L and blood counts must be performed at least every 4 weeks. The usual maintenance dosage is on average 0.5-2mg/day, but individual requirements may be much less. Should a patient require an average daily dose of less than the content of one tablet, the maintenance dose may be adjusted by introducing one or more busulfan free days between treatment days.

**NOTE:** Lower doses of MYLERAN should be used if it is administered in conjunction with other cytotoxic agents. (see Undesirable Effects and Interaction with Other Medicinal Products and other Forms of Interactions).

**Children:**

Chronic granulocytic leukaemia is rare in the paediatric age group.

Busulfan may be used to treat Philadelphia chromosome positive (Ph' positive) disease, but the Ph' negative juvenile variant responds poorly.
**Polycythaemia vera**  
The usual dosage is 4 to 6mg daily, continued for 4 to 6 weeks, with careful monitoring of the blood count, particularly the platelet count.

Further courses are given when relapse occurs; alternatively, maintenance therapy may be given using approximately half the induction dose.

If the polycythaemia is controlled primarily by venesection, short courses of MYLERAN may be given solely to control the platelet count.

**Myelofibrosis**  
The usual initial dose is 2 to 4mg daily.

Very careful haematological control is required because of the extreme sensitivity of the bone marrow in this condition.

**Essential thrombocythaemia**  
The usual dosage is 2 to 4mg per day.

Treatment should be interrupted if the total leucocyte count falls below 5 x 10^9/L or the platelet count below 500 x 10^9/L.

### 4.3 Contraindications

MYLERAN should not be used in patients whose disease has demonstrated resistance to busulfan.

MYLERAN should not be given to patients who have previously suffered a hypersensitivity reaction to busulfan or any other component of the preparation.

### 4.4 Special warnings and precautions for use

MYLERAN IS AN ACTIVE CYTOTOXIC AGENT FOR USE ONLY UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN THE ADMINISTRATION OF SUCH AGENTS.

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

MYLERAN should be discontinued if lung toxicity develops (see Undesirable Effects).

MYLERAN should not generally be given in conjunction with or soon after radiotherapy.

MYLERAN is ineffective once blast transformation has occurred.
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.

Hyperuricaemia and/or hyperuricosuria are not uncommon in patients with chronic granulocytic leukaemia and should be corrected before starting treatment with MYLERAN. During treatment, hyperuricaemia and the risk of uric acid nephropathy should be prevented by adequate prophylaxis, including adequate hydration and the use of allopurinol.

**Conventional dose Treatment:**
Patients co-administered itraconazole or metronidazole with conventional dose busulfan should be monitored closely for signs of busulfan toxicity. Weekly measurements of blood counts are recommended when co-administering these drugs (see Interaction with Other Medicinal Products and Other Forms if Interaction).

**High-dose Treatment:**
If high-dose MYLERAN is prescribed, patients should be given prophylactic anticonvulsant therapy with preferably a benzodiazepine rather than phenytoin (see Undesirable Effects and Interaction with Other Medicinal Products and Other Forms of Interaction).

Concomitant administration of itraconazole or metronidazole with high-dose busulfan has been reported to be associated with an increased risk of busulfan toxicity (see Interaction with Other Medicinal Products and Other Forms of Interaction). Co-administration of metronidazole and high dose busulfan is not recommended. Co-administration of itraconazole with high dose busulfan should be at the discretion of the prescribing physician and should be based on a risk/benefit assessment.

Hepatic veno-occlusive disease is a major complication that can occur during treatment with busulfan. 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).

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.

**Monitoring:**
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 also Undesirable Effects)

**Mutagenicity:**
Various chromosome aberrations have been noted in cells from patients receiving busulfan.

**Carcinogenicity:**
On the basis of short-term tests, MYLERAN has been classified as potentially carcinogenic by the IARC.

The World Health Association has concluded that there is a causal relationship between MYLERAN exposure and cancer.

Widespread epithelial dysplasia has been observed in patients treated with long-term MYLERAN, with some of the changes resembling precancerous lesions.

A number of malignant tumours have been reported in patients who have received MYLERAN treatment.

The evidence is growing that MYLERAN, in common with other alkylating agents, is leukaemogenic. In a controlled prospective study in which 2 years' MYLERAN treatment was given as an adjuvant to surgery for lung cancer, long-term follow up showed an increased incidence of acute leukaemia compared with the placebo-treated group. The incidence of solid tumours was not increased.

Although acute leukaemia is probably part of the natural history of polycythaemia vera, prolonged alkylating agent therapy may increase the incidence.

Very careful consideration should be given to the use of busulfan for the treatment of polycythaemia vera and essential thrombocythaemia in view of the drug's carcinogenic potential. The use of busulfan for these indications should be avoided in younger or asymptomatic patients. If the drug is considered necessary treatment courses should be kept as short as possible.

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

### 4.5 Interaction with other medicines and other forms of interaction
Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see Special Warnings and Precautions for Use).

The effects of other cytotoxics producing pulmonary toxicity may be additive.

The administration of phenytoin to patients receiving high-dose MYLERAN may result in a decrease in the myeloblative effect.
In patients receiving high-dose busulfan it has been reported that co-administration of itraconazole decreases clearance of busulfan by approximately 20% with corresponding increases in plasma busulfan levels. Metronidazole has been reported to increase trough levels of busulfan by approximately 80%. Fluconazole had no effect on busulfan clearance. Consequently, high-dose busulfan in combination with itraconazole or metronidazole is reported to be associated with an increased risk of busulfan toxicity (see Special Warnings and Precautions for Use).

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.

In paediatric population, for the combined Busulfan-Melphalan (BuMel) regimen it has been reported that the administration of melphalan less than 24 hours after the last oral busulfan administration may influence the development of toxicities.

4.6 Fertility, pregnancy and lactation

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

The use of MYLERAN should be avoided whenever possible during pregnancy, particularly during the first trimester. In every individual case the expected benefit of treatment to the mother must be weighed against the possible risks to the foetus.

A few cases of congenital abnormalities, not necessarily attributable to busulfan, have been reported and third trimester exposure may be associated with impaired intrauterine growth. However, there have also been many reported cases of apparently normal children born after exposure to MYLERAN in utero, even during the first trimester.

Studies of busulfan treatment in animals have shown reproductive toxicity (see Preclinical Safety Data). The potential risk for humans is largely unknown.

It is not known whether MYLERAN or its metabolites are excreted in human breast milk. Mothers receiving MYLERAN should not breast feed their infants.

It may cause sterility in both sexes. In women busulfan may cause severe and persistent ovarian failure, including failure to achieve puberty after administration to young girls and pre-adolescents at high-dose. It may also cause male infertility, azoospermia and testicular atrophy in male patients receiving busulfan.

4.7 Effects on ability to drive and use machines

There are no data on the effect of busulfan on driving performance or the ability to operate machinery. A detrimental effect on these activities cannot be predicted from the pharmacology of the medicine.
4.8 Undesirable effects
For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the dose received and also when given in combination with other therapeutic agents.

The following convention has been utilised for the classification of frequency: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (< 1/10,000).

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Common: Secondary acute leukaemia (see Warnings and Precautions; Carcinogenicity).

Blood and lymphatic system disorders
Very common: Dose-related bone marrow depression, manifest as leucopenia and particularly thrombocytopenia.
Rare: Aplastic anaemia.

Aplastic anaemia (sometimes irreversible) has been reported rarely, typically following long-term conventional doses and also high doses of busulfan.

Nervous system disorders
Rare: Convulsions at high dose (see Interaction with Other Medicinal Products and Other Forms of Interaction and Special Warnings and Precautions for Use).

Very rare: Myasthenia gravis.

Eye disorders
Rare: Lens changes and cataracts, which may be bilateral; corneal thinning reported after bone marrow transplantation preceded by high-dose busulfan treatment.

Cardiac disorders
Common: Cardiac tamponade in patients with thalassaemia receiving high-dose busulfan.

Respiratory, thoracic and mediastinal disorders
Very common: Idiopathic pneumonia syndrome following high dose use.

Common: Interstitial pneumonitis following long term conventional dose use.

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 may cause additive lung toxicity (see Interaction with Other Medicinal Products and Other Forms of Interaction). It is possible that subsequent radiotherapy can augment subclinical lung injury caused by busulfan. Once pulmonary toxicity is established the prognosis is poor despite busulfan 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 busulfan 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 diffuse 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.

Gastrointestinal disorders

Very common: Gastro-intestinal effects such as nausea and vomiting, diarrhoea and oral ulceration at high-dose.

Rare: Gastro-intestinal effects such as nausea and vomiting, diarrhoea and oral ulceration at conventional dose, may possibly be ameliorated by using divided doses.

Not Known Tooth hypoplasia

Gastrointestinal disorders

In paediatric transplant recipients, dental developmental anomalies (such as tooth hypoplasia, microdontia and absence of permanent teeth) have been observed with busulfan-based conditioning regimens.
Hepatobiliary disorders

Very common: Hyperbilirubinaemia, jaundice, hepatic veno-occlusive disease (see Special Warnings and Precautions for Use and Interaction with Other Medicinal Products and Other Forms of Interaction) and centrilobular sinusoidal fibrosis with hepatocellular atrophy and necrosis at high-dose.

Rare: Cholestatic jaundice and liver function abnormalities, at conventional dose. Centrilobular sinusoidal fibrosis.

Busulfan is not generally considered to be significantly hepatotoxic at normal therapeutic doses. However, retrospective review of post mortem reports of patients who had been treated with low-dose busulfan for at least two years for chronic granulocytic leukaemia showed evidence of centrilobular sinusoidal fibrosis.

Skin and subcutaneous tissue disorders

Common: Alopecia at high-dose.
Hyperpigmentation (see also General disorders and administration site conditions).

Rare: Alopecia at conventional dose, skin reactions including urticaria, erythema multiforme, erythema nodosum, porphyria cutanea tarda, an allopurinol-type rash and excessive dryness and fragility of the skin with complete anhydrosis, dryness of oral mucous membranes and cheilosis, Sjögren’s syndrome. An increased cutaneous radiation effect in patients receiving radiotherapy soon after high-dose busulfan.

Hyperpigmentation occurs, particularly in those with a dark complexion. It is often most marked on the neck, upper trunk, nipples, abdomen and palmar creases. This may also occur as part of a clinical syndrome (see General disorders and administration site conditions).

Renal and urinary disorders

Common: Haemorrhagic cystitis at high dose in combination with cyclophosphamide.

Reproductive system and breast disorders

Very common: Ovarian suppression and amenorrhoea with menopausal symptoms in pre-menopausal patients at high-dose; severe and persistent ovarian failure, including failure to achieve puberty.
after administration to young girls and pre-adolescents at high-dose. Sterility, azoospermia and testicular atrophy in male patients receiving busulfan.

Uncommon: Ovarian suppression and amenorrhoea with menopausal symptoms in pre-menopausal patients at conventional dose. In very rare cases, recovery of ovarian function has been reported with continuing treatment.

Very rare: Gynecomastia.

Studies of busulfan treatment in animals have shown reproductive toxicity (see Pre-clinical Safety Data).

General disorders and administration site conditions

Very rare: Clinical syndrome# (weakness, severe fatigue, anorexia, weight loss, nausea and vomiting and hyperpigmentation of the skin) resembling adrenal insufficiency (Addison’s disease) but without biochemical evidence of adrenal suppression, mucous membrane hyperpigmentation or hair loss (see Skin and subcutaneous tissue disorders).

Rare: Widespread dysplasia of epithelia.

#Seen in a few cases following prolonged busulfan therapy. The syndrome has sometimes resolved when busulfan has been withdrawn.

Many histological and cytological changes have been observed in patients treated with busulfan, 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.

**Reporting of suspected adverse reactions**
Healthcare professionals are asked to report any suspected adverse reactions [https://nzphvc.otago.ac.nz/reporting/](https://nzphvc.otago.ac.nz/reporting/)

4.9 **Overdose**

**Symptoms and signs:**
The acute dose-limiting toxicity of MYLERAN in man is myelosuppression (see Undesirable Effects). The main effect of chronic overdosage is bone marrow depression and pancytopenia.

**Treatment:**
There is no known antidote. Dialysis should be considered in the management of overdose as there is one report of successful dialysis of busulfan.

Appropriate supportive treatment should be given during the period of haematological toxicity.

Since, busulfan is metabolised through conjugation with glutathione, administration of glutathione might be considered.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mode of Action:
Busulfan (1,4-butanediol dimethanesulfonate) 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. Although not curative, MYLERAN is very effective in reducing the total granulocyte mass, relieving the symptoms of disease and improving the clinical state of the patient. MYLERAN has been shown to be superior to splenic irradiation when judged by survival times and maintenance of haemoglobin levels and is as effective in controlling spleen size.

5.2 Pharmacokinetic Properties

Absorption:
The bioavailability of oral busulfan shows large intra-individual variation ranging from 47% to 103% (mean 68%) in adults.

The area under the curve (AUC) and peak plasma concentrations (Cmax) of busulfan have been shown to be linearly dose dependent. Following administration of a single 2 mg oral dose of busulfan, the AUC and Cmax of busulfan were 125±17 nanograms.h/ml and 28±5 nanograms/ml respectively. A lag time between busulfan administration and detection in the plasma of up to 2 h has been reported.

High-dose Treatment:
Busulfan was assayed either using gas liquid chromatography with electron capture detection or by high-performance liquid chromatography (HPLC).

Following oral administration of high dose busulfan (1 mg/kg every 6 h for 4 days), AUC and Cmax in adults are highly variable but have been reported to be 8260
nanograms.h/ml (range 2484 to 21090) and 1047 nanograms/ml (range 295 to 2558) respectively when measured by HPLC and 6135 nanograms.h/ml (range 3978 to 12304) and 1980 nanograms/ml (range 894 to 3800) respectively using gas chromatography.

**Distribution:**
Busulfan is reported to have a volume of distribution of 0.64±0.12 L/kg in adults.

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 busulfan to blood cells and plasma proteins has been reported to be 47% and 32%, respectively.

**Metabolism and Excretion:**
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.

Busulfan has a mean elimination half life of between 2.3 and 2.8 h. Adult patients have demonstrated a clearance of busulfan of 2.4 to 2.6 ml/min/kg. The elimination half life of busulfan has been reported to decrease upon repeat dosing suggesting that busulfan potentially increases its own metabolism.

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

**Special Patient Populations**
**Children**
The bioavailability of oral busulfan shows large intra-individual variation ranging from 22% to 120% (mean 80%) 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/m² every 6 h for 4 days the ratio was 1.39:1.

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

5.3 Preclinical safety data

**Mutagenicity:**
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.

**Carcinogenicity:**
There is insufficient evidence from preclinical studies to determine whether busulfan has carcinogenic potential (see Special Warnings and Special Precautions for Use).

**Teratogenicity:**
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.

**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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

**Tablet core:**
Anhydrous lactose
Pregelatinised starch
Magnesium stearate

**Tablet coating:**
Hyromellose
Titanium dioxide
Triacetin

6.2 Incompatibilities
None known

6.3 Shelf-life
36 months

6.4 Special precautions for storage
Store below 25ºC. Keep dry.

6.5 Nature and contents of container
MYLERAN 2mg tablets are white, film-coated, round, biconvex tablets engraved “GX EF3” on one side and “M” on the other, supplied in amber glass bottles with a child resistant closure containing 100 tablets.

6.6 Special precautions for disposal
The tablets should not be divided and provided the outer coating is intact, there is no risk in handling MYLERAN tablets.

Handlers of MYLERAN tablets should follow guidelines for the handling of cytotoxic agents according to prevailing local recommendations and/or regulations.

Disposal:
MYLERAN tablets surplus to requirements should be destroyed in a manner appropriate to the prevailing local regulations for the destruction of dangerous substances.

7. MEDICINE SCHEDULE
Prescription Only Medicine

8. SPONSOR
Pharmacy Retailing Pty Ltd
Trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand
Ph: (09) 915 9500
Email: aspen@aspenpharma.co.nz

9. DATE OF FIRST APPROVAL
16 August 2004

10. DATE OF REVISION OF THE TEXT
16th September 2020

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SUMMARY TABLE OF CHANGES

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